1-DEOXY BACCATIN III, 1-DEOXY TAXOL AND 1-DEOXY TAXOL ANALOGS AND METHOD FOR THE PREPARATION THEREOF

This invention was made with Government support under NIH Grant #CA 42031 awarded by the National Institutes of Health. The Government has certain rights in the invention.

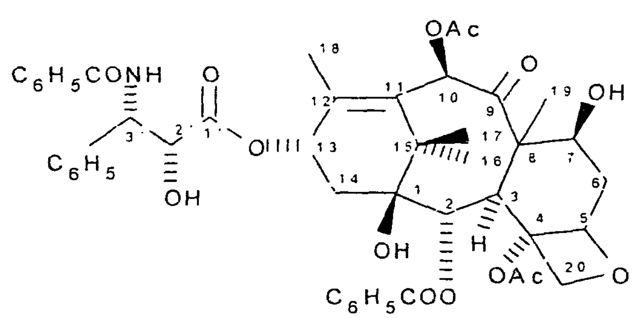
REFERENCE TO RELATED APPLICATION

This application claims priority, at least in part, from Provisional Application Serial No. 60/016,927, filed May 6, 1996.

BACKGROUND OF THE INVENTION

The present invention is directed to novel taxanes which have utility as antitumor agents and to a process for their preparation.

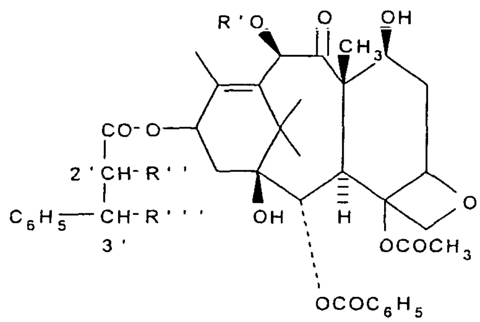
The taxane family of terpenes, of which baccatin III and taxol are members, has attracted considerable interest in both the biological and chemical arts. Taxol is a promising cancer chemotherapeutic agent with a broad spectrum of tumor-inhibiting activity. Taxol has a 2'R, 3'S configuration and the following structural formula:



(I)

wherein Ac is acetyl. Because of this promising activity, taxol is currently undergoing clinical trials in both France and the United States.

Colin et al. reported in U.S. Pat. No. 4,814,470 that taxol derivatives having the structural formula (II) below, have an activity significantly greater than that of taxol (I).



(II)

R' represents hydrogen or acetyl and one of R" and R''' represents hydroxy and the other represents tert-butoxycarbonylamino and their stereoisomeric forms, and mixtures thereof. The compound of this formula in which R" is hydroxy, R''' is tert-butoxycarbonylamino having the 2'R, 3'S configuration is commonly referred to as taxotere.

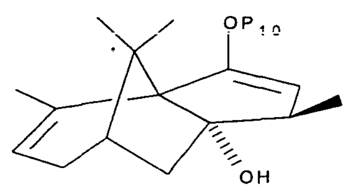
Although taxol and taxotere are promising chemotherapeutic agents, they are not universally effective. Accordingly, a need remains for additional chemotherapeutic agents.

SUMMARY OF THE INVENTION

Among the objects of the present invention, therefore, is the provision of novel taxanes which are valuable anti-tumor agents and a process for their preparation.

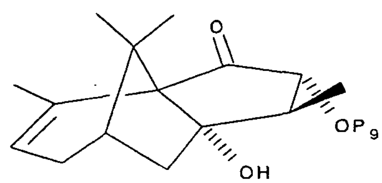
Briefly, therefore, the present invention is directed to a process for the preparation of 1-deoxy baccatin III, 1-deoxy taxol and 1-deoxy taxol analogs. The process comprises at least one of the following steps:

(a) reacting a compound having the formula:



[3]

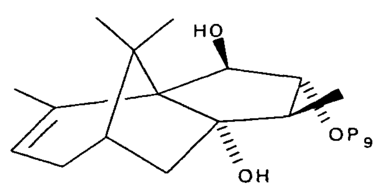
with a peracid such as metachloroperbenzoic acid to form a compound having the formula:



[4];

wherein P_{10} is a silyl hydroxy protecting group such as triethylsilyl or an acyl group such as benzoyl. In this reaction, the protected hydroxy group $-OP_{10}$ migrates to the adjacent carbon and becomes $-OP_9$ with P_9 being the same as P_{10};

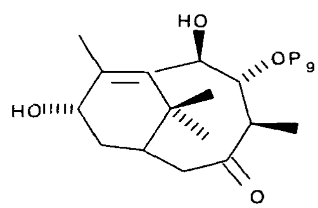
(b) subjecting a compound having the formula:



[5]

to an epoxy alcohol fragmentation consisting of (ia) epoxidation of an olefinic residue with a

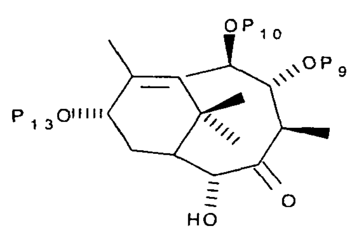
hydroperoxide, preferably t-BuOOH, in the presence of a transition metal catalyst, preferably titanium tetraisopropoxide, or (ib) treatment of the olefinic residue with a peracid such as peracetic acid followed by (ii) addition of a sulfide, preferably dimethyl sulfide, followed by heating in the presence of a transition metal catalyst, preferably titanium tetraisopropoxide, to form a compound having the formula:



[6];

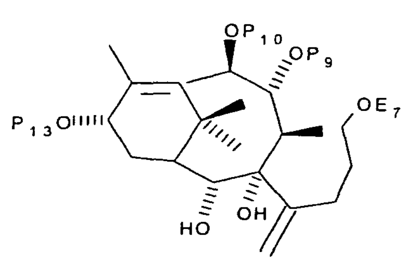
wherein P_9 is a hydroxyl protecting group such as a silyl group, ketal, acetal, or ether which does not contain a reactive functionality;

(c) reacting a compound having the formula:



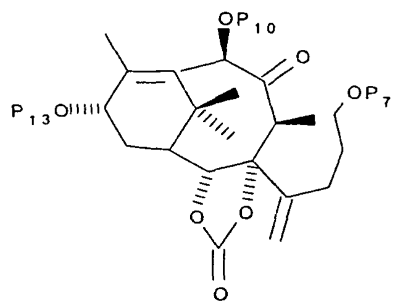
[9]

with a vinyl organometallic reagent to form a compound having the formula:



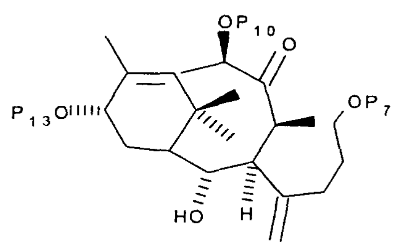
[10];

(d) reacting a compound having the formula:



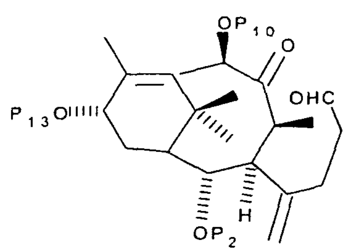
[14]

with a paladium catalyst to form a compound having the formula:



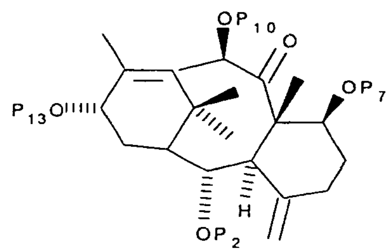
[15]

(e) reacting a compound having the formula:



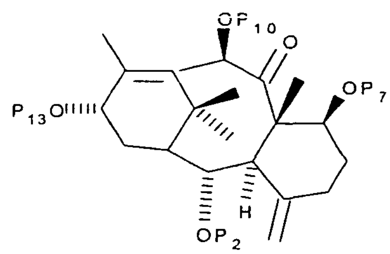
[17]

with a base, most preferably BaO in methanol, and protecting the C7 hydroxy substituent, for example, by reacting the product with TESOTf, to form a compound having the formula:



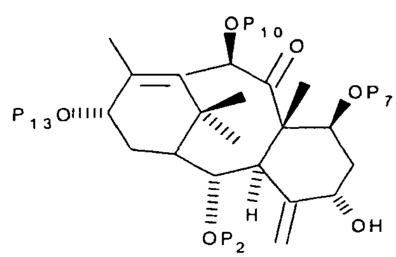
[18]; and

(f) reacting a compound having the formula:



[18]

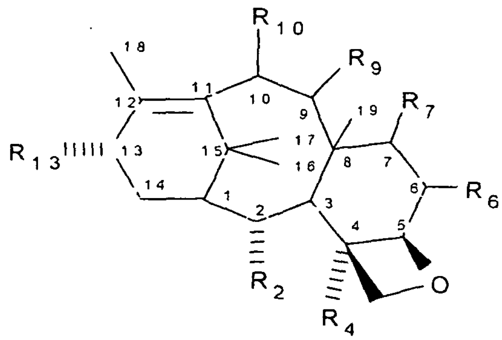
with SeO_2 to form a compound having the formula:



[19];

wherein E_7 is hydrogen or a hydroxy protecting group, and P_2, P_7, P_9, P_{10} and P_{13} are hydroxy protecting groups as hereinafter defined.

In general, the process of the present invention may be used to prepare 1-deoxy baccatin III, 1-deoxy taxol and 1-deoxy taxol analogs having the formula:



wherein

M comprises ammonium or is a metal;

R_2 is $-OT_2$, $-OCOZ_2$, or $-OCOOZ_2$;

R_4 is $-OT_4$, $-OCOZ_4$, or $-OCOOZ_4$;

R_6 is hydrogen, keto, $-OT_6$, $-OCOZ_6$ or $-OCOOZ_6$;

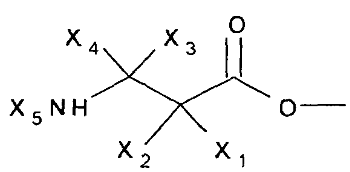
R_7 is hydrogen, halogen, $-OT_7$, $-OCOZ_7$ or $-OCOOZ_7$;

R_9 is hydrogen, keto, $-OT_9$, $-OCOZ_9$ or $-OCOOZ_9$;

R_{10} is hydrogen, keto, $-OT_{10}$, $-OCOZ_{10}$ or $-OCOOZ_{10}$;

R_6, R_7, R_9, and R_{10} independently have the alpha or beta stereochemical configuration;

R_{13} is hydroxy, protected hydroxy, keto, MO- or



;

T_2, T_4, T_6, T_7, T_9 and T_{10} are independently hydrogen or hydroxy protecting group;

X_1 is $-OX_6$;

X_2 is hydrogen, hydrocarbon, heterosubstituted hydrocarbon, or heteroaryl;

X_3 and X_4 are independently hydrogen, hydrocarbon, heterosubstituted hydrocarbon, or heteroaryl;

X_5 is $-COX_{10}$, $-COOX_{10}$, $-COSX_{10}$, or $-CONX_8X_{10}$;

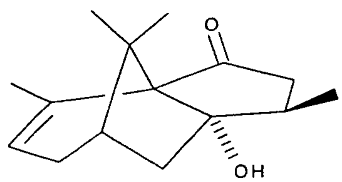
X_6 is hydrogen, hydrocarbon, heterosubstituted hydrocarbon, heteroaryl, or hydroxy protecting group or a functional group which increases the water solubility of the taxane derivative;

X_8 is hydrogen, hydrocarbon, heterosubstituted hydrocarbon;

X_{10} is hydrocarbon, heterosubstituted hydrocarbon, or heteroaryl; and

Z_2, Z_4, Z_6, Z_7, Z_9 and Z_{10} are independently hydrocarbon, heterosubstituted hydrocarbon, or heteroaryl.

The present invention is additionally directed to compounds having the formulae



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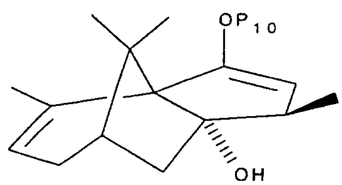

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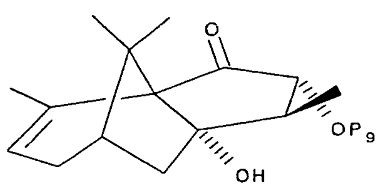

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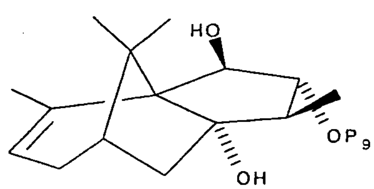

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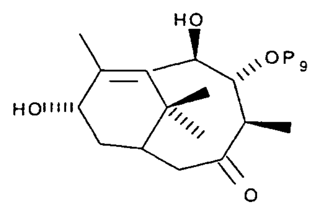

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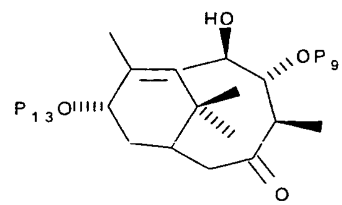

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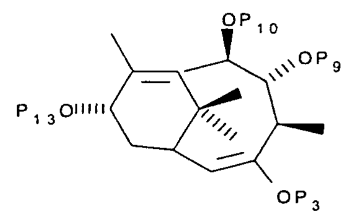

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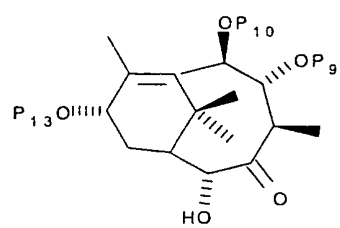

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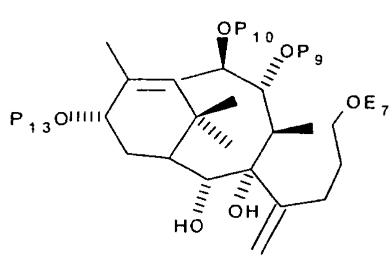

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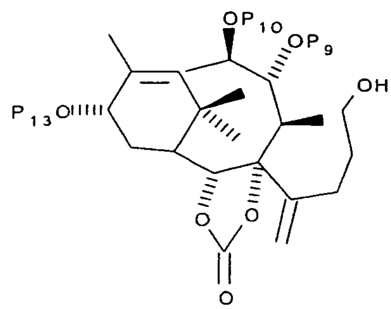
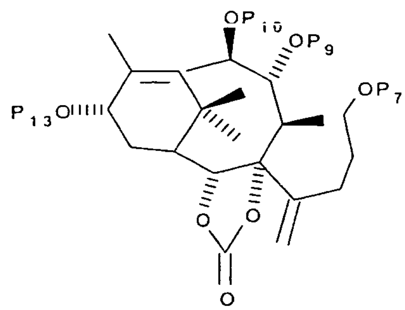
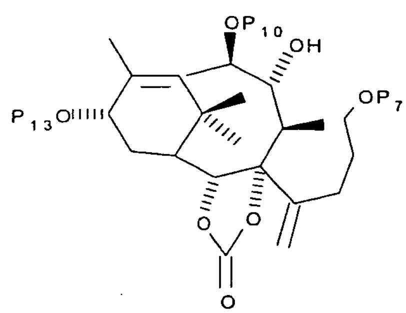

OP10
OP9
OH
P13O
O
O
O

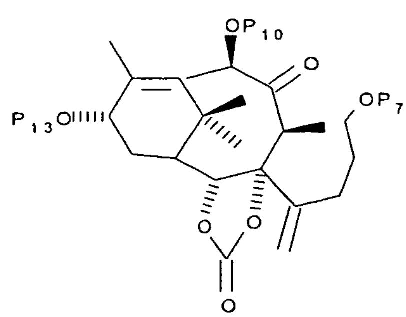
[11]


OP10
OP9
OP7
P13O
O
O
O

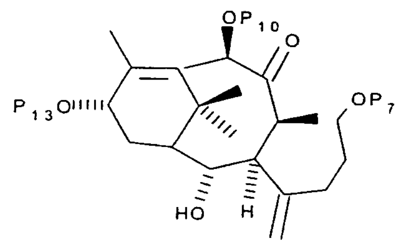
[12]


OP10
OH
OP7
P13O
O
O
O

[13]


OP10
O
OP7
P13O
O
O
O

[14]



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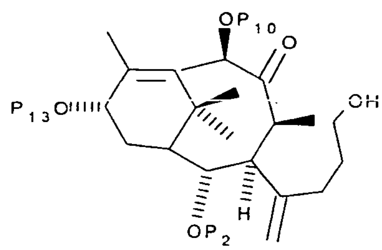

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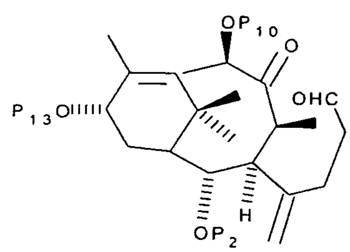

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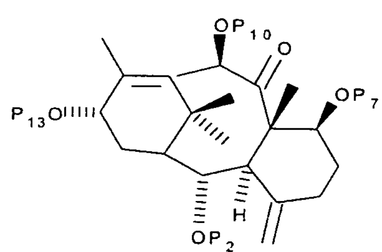

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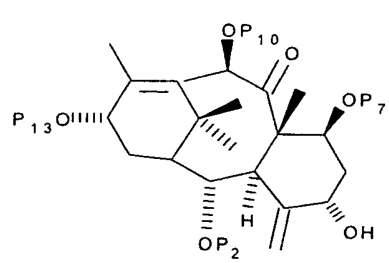

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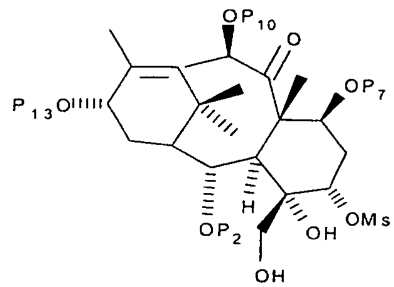
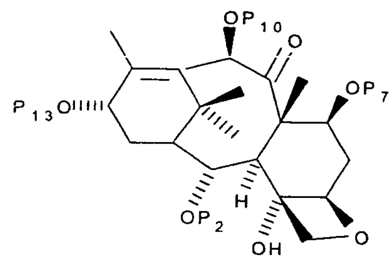


[20]



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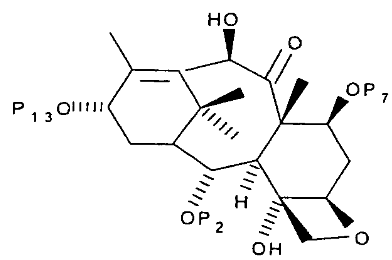

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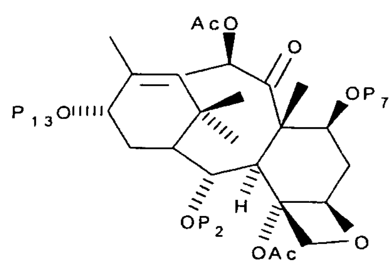

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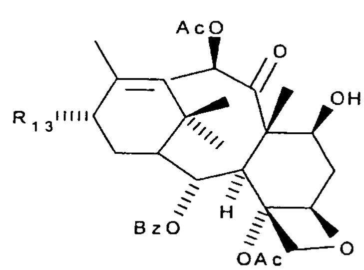
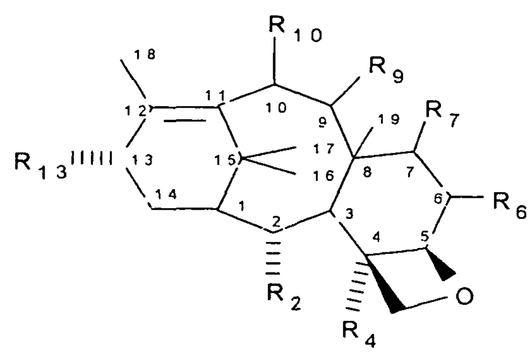


wherein E_7 is hydrogen or a hydroxy protecting group; Bz is benzoyl; P_2, P_3, P_7, P_9, P_{10} and P_{13} are hydroxy protecting groups; and R_{13} is as previously defined. These compounds are key intermediates in the synthesis of 1-deoxy baccatin III, 1-deoxy taxol and other analogs. The present invention is also directed to processes for the preparation of these key intermediates.

Other objects and features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The process of the present invention enables the preparation of 1-deoxy taxol, 1-deoxy taxotere and analogs of 1-deoxy taxol and 1-deoxy taxotere from 1-deoxy baccatin III, 1-deoxy-10-deactylbaccatin III, or analogs thereof. In a preferred embodiment, these compounds have the formula:



wherein

M comprises ammonium or is a metal;

R_2 is $-OCOZ_2$;

R_4 is $-OCOZ_4$;

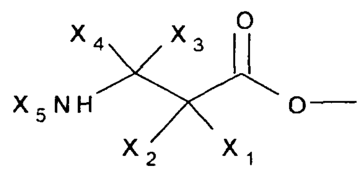
R_6 is hydrogen;

R_7 is hydrogen, $-OT_7$, or $-OCOZ_7$;

R_9 is hydrogen, keto, $-OT_9$, $-OCOZ_9$;

R_{10} is hydrogen, keto, $-OT_{10}$, or $-OCOZ_{10}$;

R_{13} is MO- or



;

T_7, T_9 and T_{10} are independently hydrogen or hydroxy protecting group;

X_1 is $-OX_6$;

X_2 is hydrogen;

X_3 is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, or heteroaryl;

X_4 is hydrogen;

X_5 is $-COX_{10}$ or $-COOX_{10}$;

X_6 is hydrogen or hydroxy protecting group;

X_{10} is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, phenyl, substituted phenyl, or heteroaryl; and

Z_2 is alkyl, substituted alkyl, phenyl, substituted phenyl, or heteroaryl;

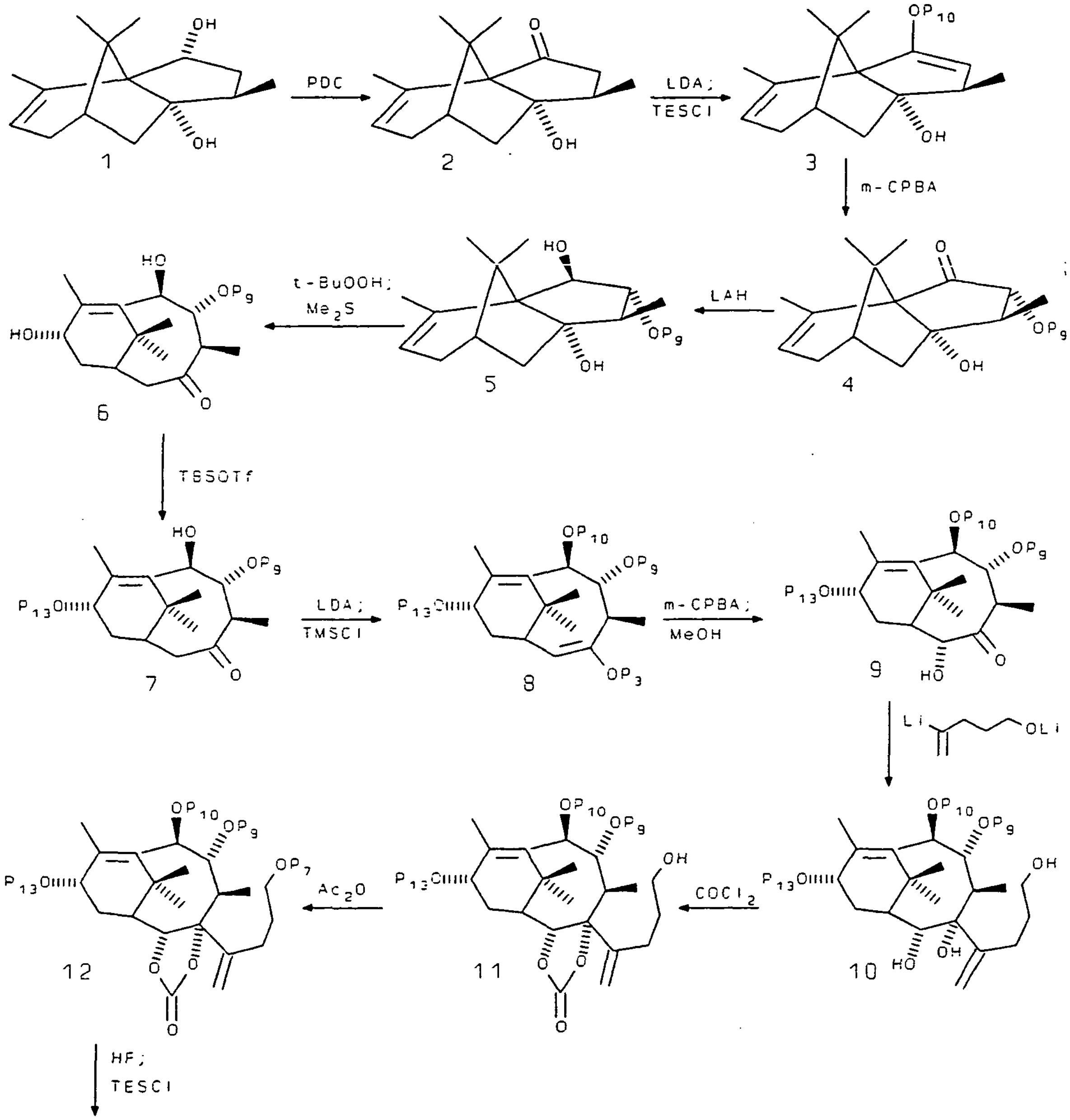
Z_4 is phenyl, substituted phenyl, or heteroaryl; and

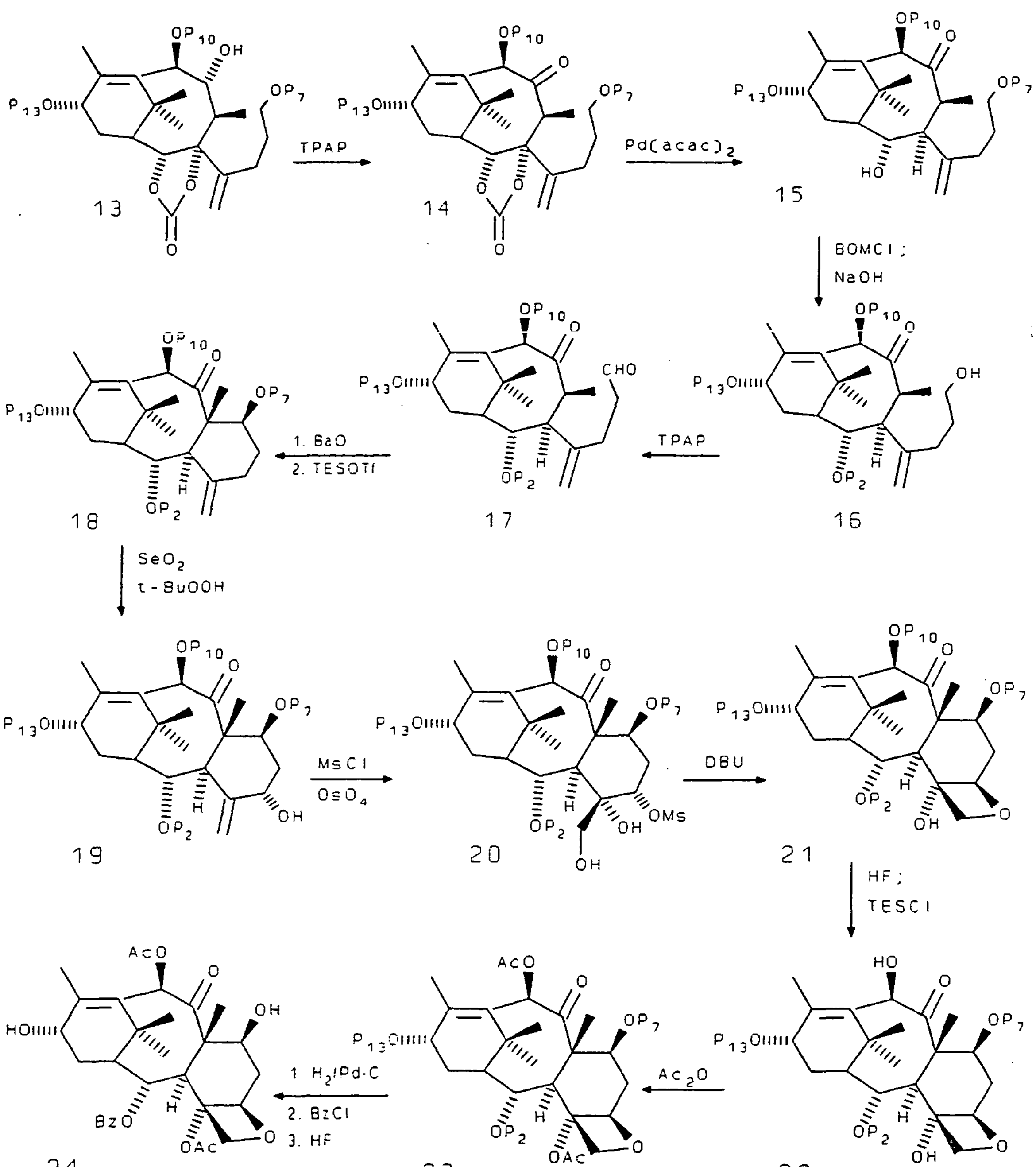
Z_7, Z_9 and Z_{10} are independently alkyl, substituted alkyl, phenyl, substituted phenyl, or heteroaryl.

An exemplary synthesis of 1-deoxy baccatin III is depicted in Reaction Scheme **1**. The starting material, diol **1**, can be prepared from patchino (commonly known as B-patchouline epoxide) which is commercially available. The patchino is first reacted with an organo-metallic, such as lithium t-butyl followed by oxidation with an organic peroxide, such as t-butylperoxide in the presence

of titanium tetraisopropoxide to form a tertiary alcohol. The tertiary alcohol is then reacted with a Lewis acid, such as boron trifluoride at low temperature, in the range from 40°C to -100°C; in the presence of an acid, such as trifluoromethane sulfonic acid. A graphical depiction of this reaction scheme along with an experimental write-up for the preparation of diol **1** can be found in U.S. Patent No. 4,876,399.

REACTION SCHEME 1





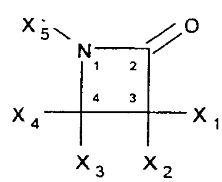
13 14 15 16 17 18 19 20 21 22 23 24

1-Deoxy-Baccatin III

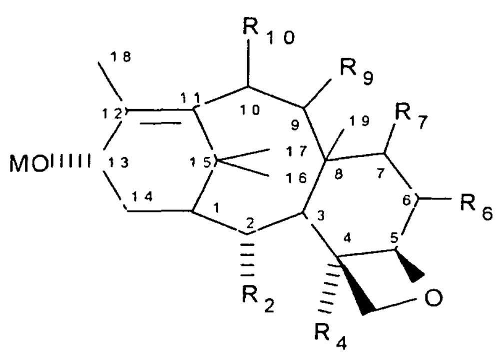
In this reaction scheme, P_2 is BOM; P_3 is TMS; P_7 is Ac in compounds 12-15 and TES in compounds 18-23; P_9 is TES in

compounds 4, 5, 6 and 7, and TMS in compounds 8, 9, 10, 11 and 12; P_{10} is TES, and P_{13} is TBS in compounds 7 through 21 and TES in compounds 22 and 23. It should be understood, however, that P_2, P_3, P_7, P_9, P_{10}, and P_{13} may be other hydroxy protecting groups.

In general, tetracyclic taxanes bearing C13 side chains may be obtained by reacting a ß-lactam with alkoxides having the taxane tetracyclic nucleus and a C-13 metallic or ammonium oxide substituent to form compounds having a ß-amido ester substituent at C-13. The ß-lactams have the following structural formula:



wherein X_1 - X_5 are as defined above. The alkoxides having the tetracyclic taxane nucleus and a C-13 metallic oxide or ammonium oxide substituent have the following structural formula:



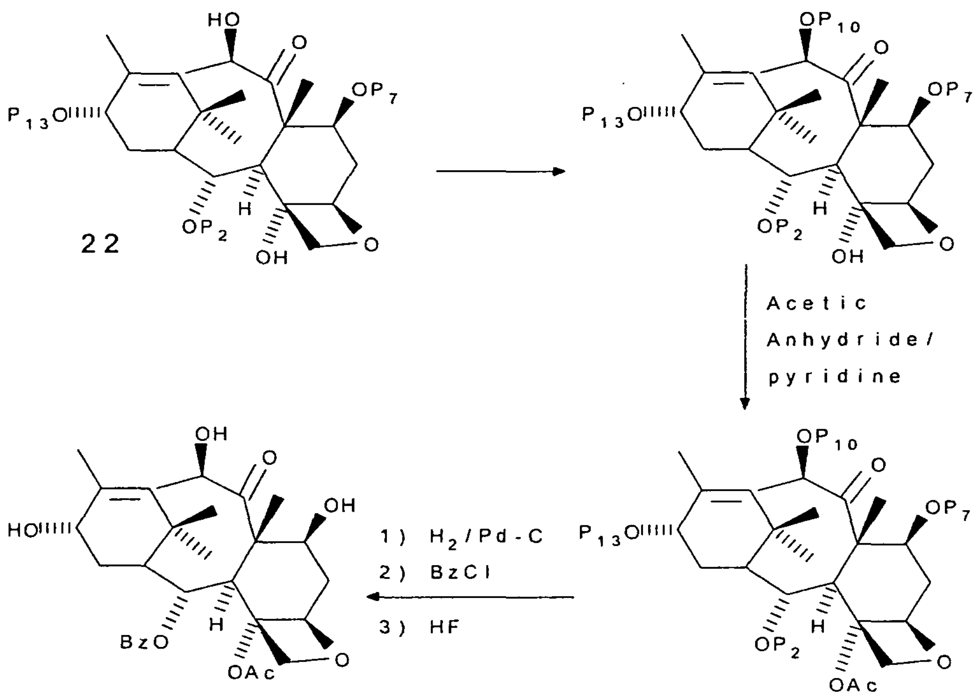
wherein R_2, R_4, R_6, R_7, R_9, R_{10} and R_{13} are as previously defined and M comprises ammonium or is a metal optionally selected from Group IA, IIA, transition (including lanthanides and actinides), IIB, IIIA, IVA, VA, or VIA

metals (CAS version). If M comprises ammonium, it is preferably tetraalkylammonium and the alkyl component of the tetraalkylammonium substituent is preferably C_1 - C_{10} alkyl such as methyl or butyl.

1-Deoxytaxol may be prepared by protecting the C7 hydroxy group of 1-deoxy Baccatin III **24** with a suitable hydroxy protecting group, converting the 7-protected Baccatin III to the corresponding alkoxide and reacting the alkoxide with a β-lactam in which X_1 is protected hydroxy, X_3 is phenyl, X_5 is benzoyl and X_2 and X_4 are hydrogen. Protecting groups such as 2-methoxypropyl ("MOP"), 1-ethoxyethyl ("EE"), benzyloxymethyl are preferred, but a variety of other standard protecting groups such as trialkyl and triaryl silyl groups may be used.

1-Deoxytaxotere may be prepared in the same manner as 1-deoxytaxol except that 1-deoxy-10-deacetylbaccatin III is used instead of 1-deoxybaccatin III and X_5 of the β-lactam is t-butoxycarbonyl instead of benzoyl. 1-deoxy-10-deacetyl-baccatin III may be prepared as set forth in Reaction Scheme 2, starting with compound **22**.

REACTION SCHEME 2



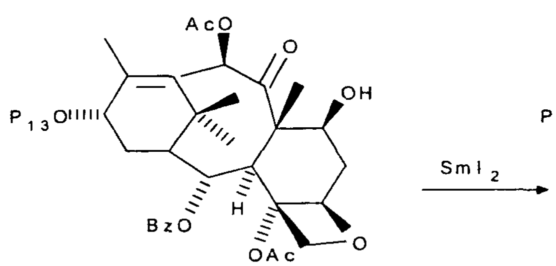
1-Deoxy-10-deacetyl
Baccatin III

Analogs of 1-deoxy taxol and 1-deoxytaxotere bearing alternative side chain subsituents may be prepared by using other suitably substituted β-lactams. For example, 1-deoxy taxol and 1-deoxytaxotere analogs having alkyl, alkenyl, alkynyl, substituted aryl, heteroaryl or substituted heteroaryl substituents at the C3' position are prepared using β-lactams in which X_3 is alkyl, alkenyl, alkynyl, substituted aryl, heteroaryl or substituted heteroaryl. Alternatively, X_5 of the β-lactam may be $-COX_{10}$, $-COOX_{10}$, $-COSX_{10}$ or $-CONX_8X_{10}$ wherein X_8 and X_{10} are as previously defined.

1-deoxy-10-desacetoxy analogs of taxol can be prepared from the corresponding 1-deoxy-10-desacetoxy derivatives of baccatin III and 1-deoxy-10-desoxy

derivatives of 10-DAB. These derivatives may be prepared as illustrated in Reaction Scheme 3 by reacting 1-deoxy-baccatin III or 1-deoxy-10-DAB (or their derivatives) with samarium diiodide. Reaction between the tetracyclic taxane having a C10 leaving group and samarium diiodide may be carried out at 0°C in a solvent such as tetrahydrofuran. Advantageously, the samarium diiodide selectively abstracts the C10 leaving group; C13 side chains and other substituents on the tetracyclic nucleus remain undisturbed.

REACTION SCHEME 3

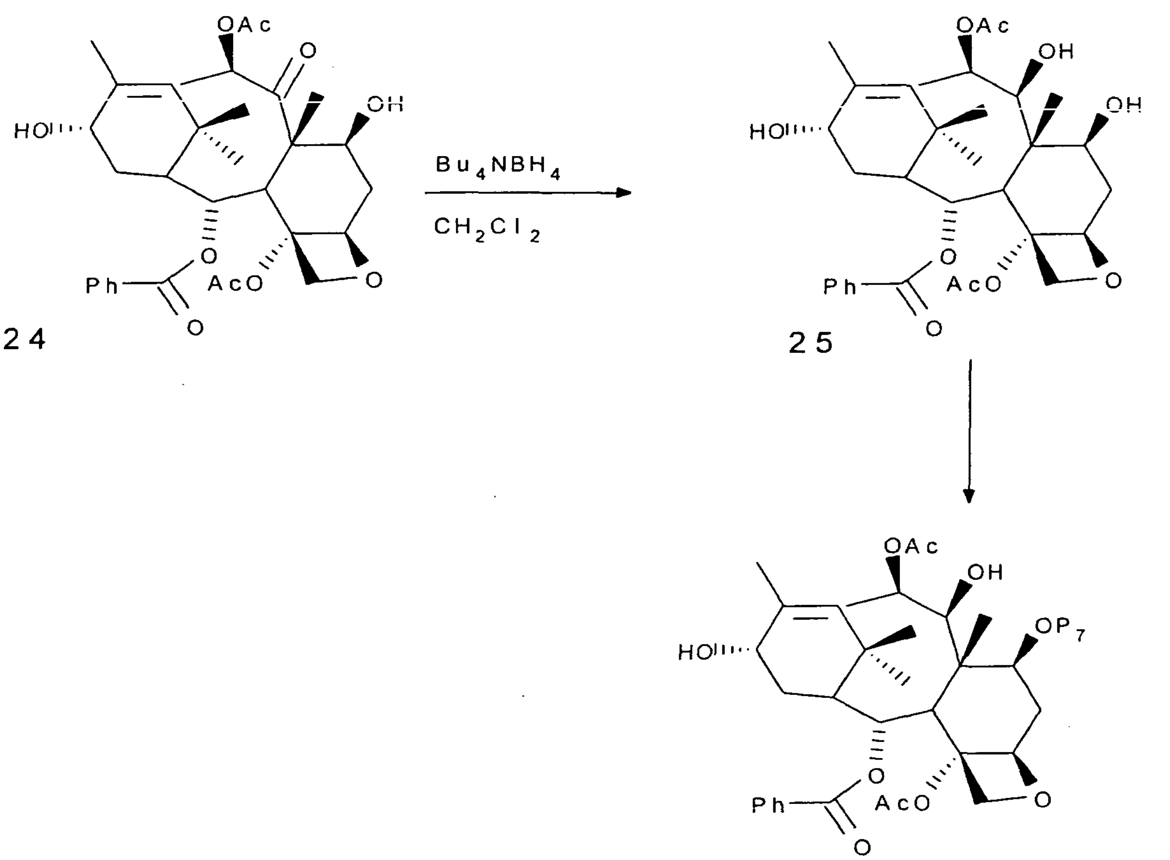


Analogs of 1-deoxy taxol and 1-deoxytaxotere having alternative C9 substituents may be prepared by selectively reducing the C9 keto substituent of 1-deoxytaxol, 1-deoxy-10-DAB, 1-deoxybaccatin III or one of the other intermediates disclosed herein to yield the corresponding 9-β-hydroxy-1-deoxy derivative. The reducing agent is preferably a borohydride and, most preferably, tetrabutylammoniumboro-hydride (Bu_4NBH_4) or triacetoxyborohydride.

As illustrated in Reaction Scheme 4, the reaction of 1-deoxybaccatin III **24** with Bu_4NBH_4 in methylene chloride yields 9-desoxo-9β-hydroxy-1-deoxybaccatin III **25**. After the C7 hydroxy group is protected with a suitable protecting group, a suitable side chain may be attached to 7-protected-9ß-hydroxy-1-

deoxy derivative **26** as elsewhere described herein. Removal of the remaining protecting groups thus yields 9β-hydroxy-desoxo-1-deoxy taxol or other 9-β-hydroxy-1-deoxytetracylic taxane having a C13 side chain.

<u>REACTION SCHEME 4</u>



24

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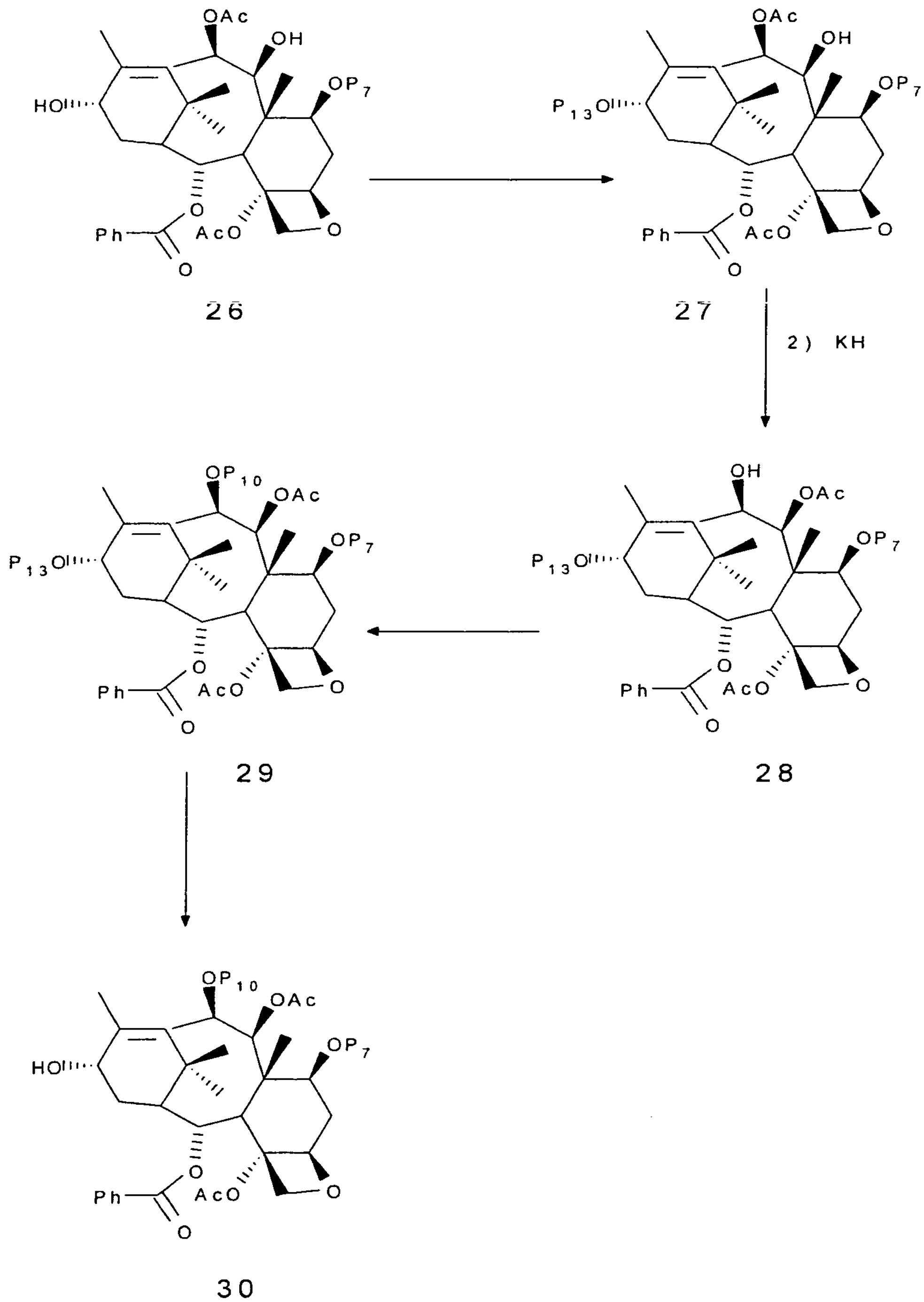
26

Alternatively, the C13 hydroxy group of 7-protected-9β-hydroxy-1-deoxy derivative **26** may be protected with a protecting group which can be selectively removed relative to the C7 hydroxy protecting group as illustrated in Reaction Scheme 5, to enable further selective manipulation of the various

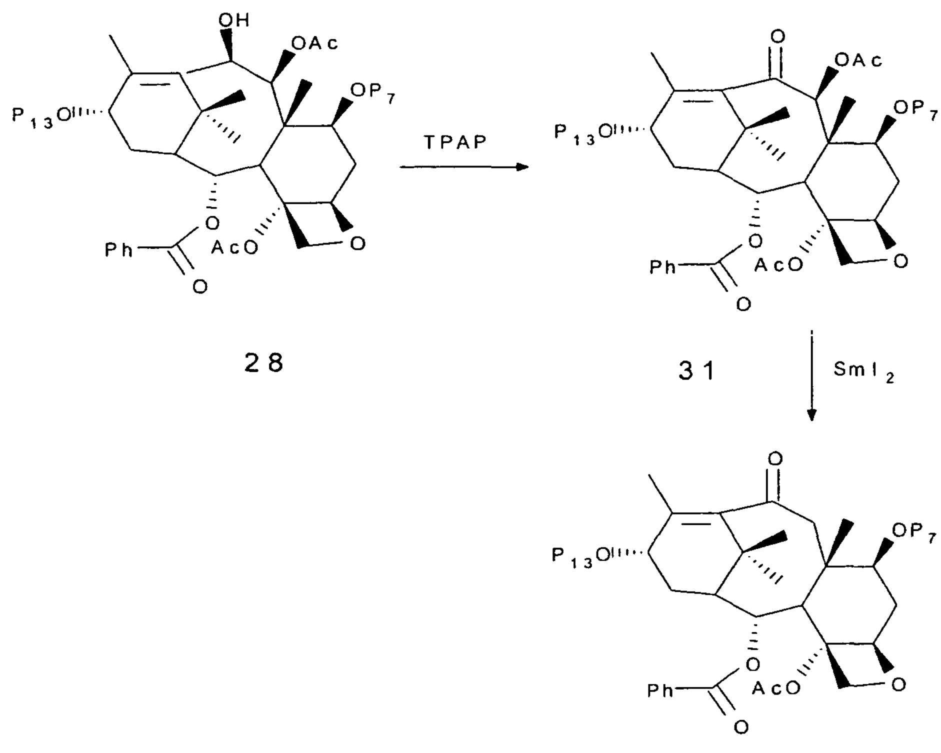
substituents of the taxane. For example, reaction of 7,13-protected-9β-hydroxy-1-deoxy derivative **27** with KH causes the acetate group to migrate from C10 to C9 and the hydroxy group to migrate from C9 to C10, thereby yielding 10-desacetyl derivative **28**. Protection of the C10 hydroxy group of 10-desacetyl derivative **28** with a protecting group yields derivative **29**. Selective removal of the C13 hydroxy protecting group from derivative **29** yields derivative **30** to which a suitable side chain may be attached as described above.

REACTION SCHEME 5



As shown in Reaction Scheme 6, 10-oxo derivative **31** can be provided by oxidation of 10-desacetyl derivative **28**. Thereafter, the C13 hydroxy protecting group can be selectively removed followed by attachment of a side chain as described above to yield 9-acetoxy-10-oxo-taxol or other 9-acetoxy-10-oxotetracylic taxanes having a C13 side chain. Alternatively, the C9 acetate group can be selectively removed by reduction of 10-oxo derivative **31** with a reducing agent such as samarium diiodide to yield 9-desoxo-10-oxo derivative **32** from which the C13 hydroxy protecting group can be selectively removed followed by attachment of a side chain as described above to yield 9-desoxo-10-oxo-1-deoxytaxol or other 9-desoxo-10-oxo-1-deoxytetracylic taxanes having a C13 side chain.

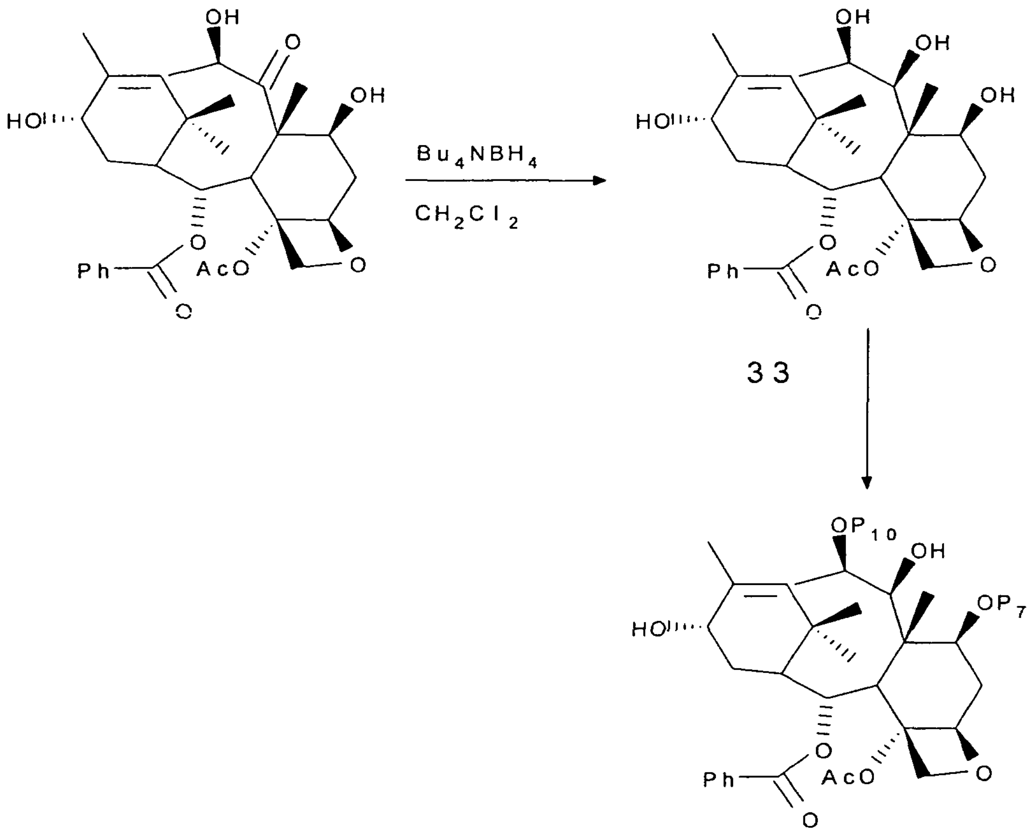
REACTION SCHEME 6



32

Reaction Scheme 7 illustrates a reaction in which 1-deoxy-10-DAB is reduced to yield tetraol **33**. The C7 and C10 hydroxyl groups of tetraol **33** can then be selectively protected with a protecting group to produce diol **34** to which a C13 side chain can be attached as described above or, alternatively, after further modification of the tetracylic substituents.

REACTION SCHEME 7



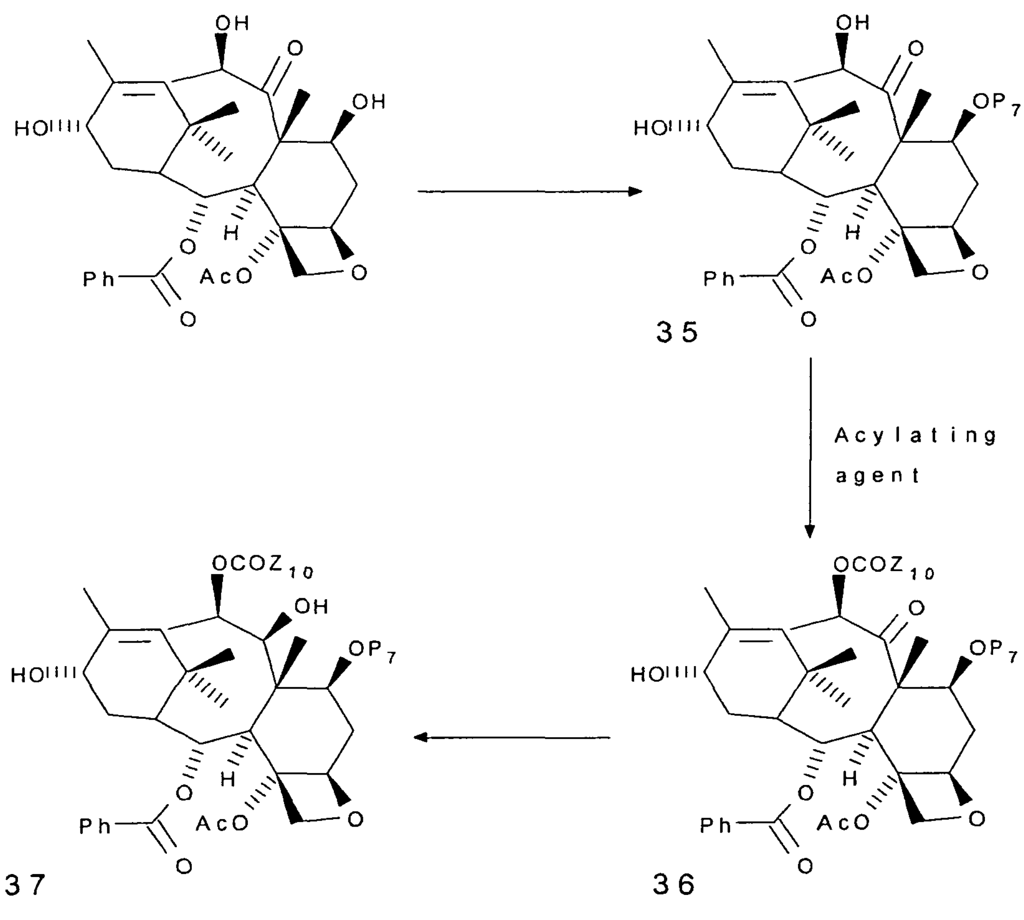
33

34

Taxanes having C9 and/or C10 acyloxy substituents other than acetoxy can be prepared using 1-deoxy-10-DAB as a starting material as illustrated in Reaction Scheme 8. After protecting the C7 hydroxy of 1-deoxy-10-DAB with a suitable protecting group to yield 7-protected 1-deoxy-10-DAB **35**, the C10 hydroxy substituent of 7-protected 1-deoxy-10-DAB **35** may then be readily acylated with any standard acylating agent such as an acid chloride to yield derivative **36** having a new C10 acyloxy substituent. Use of the analogous chloroformate instead of the acid chloride would yield the

corresponding carbonate. Deprotection of the C7 hydroxy group, followed by selective reduction of the C9 keto substituent of derivative **36** with tetrabutylammonium borohydride, and then protection of the C7 hydroxy group yields 9ß-hydroxy derivative **37** to which a C13 side chain may be attached. Alternatively, the C10 and C9 groups can be caused to migrate as set forth in Reaction Scheme **5**, above.

REACTION SCHEME 8

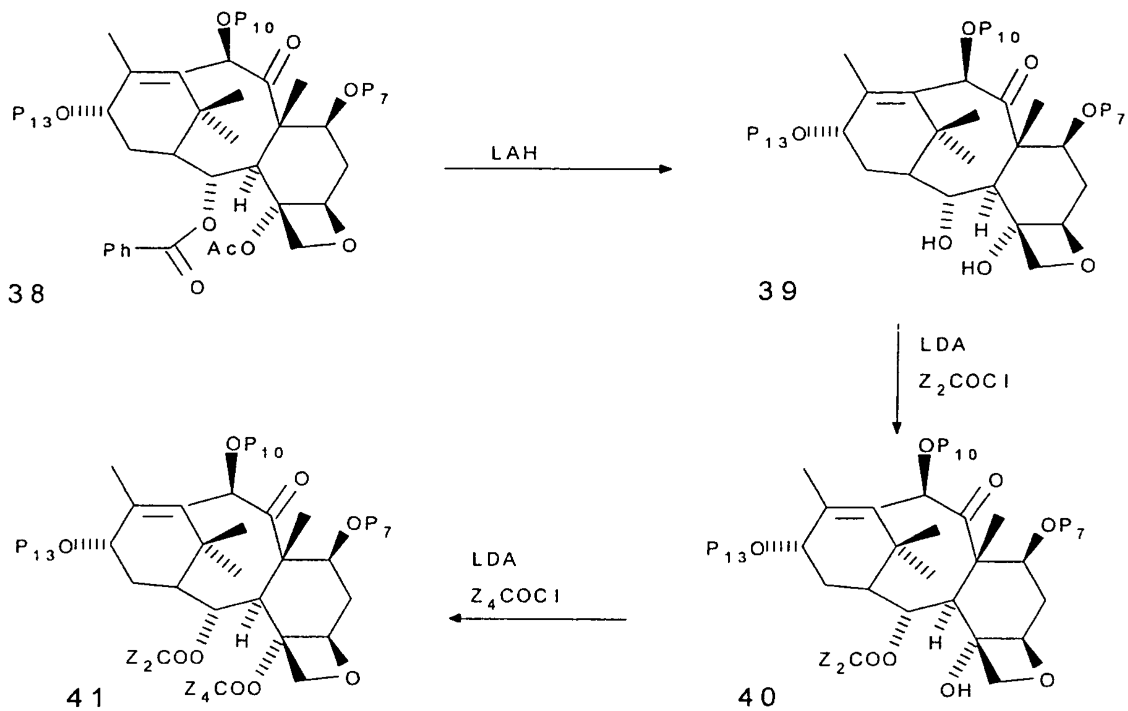


Taxanes having alternative C2 and/or C4 esters can be prepared using baccatin III and 10-DAB as starting

materials. The C2 and/or C4 esters of baccatin III and 10-DAB can be selectively reduced to the corresponding alcohol(s) using reducing agents such as LAH or Red-Al, and new esters can thereafter be substituted using standard acylating agents such as anhydrides and acid chlorides in combination with an amine such as pyridine, triethylamine, DMAP, or diisopropyl ethyl amine. Alternatively, the C2 and/or C4 alcohols may be converted to new C2 and/or C4 esters through formation of the corresponding alkoxide by treatment of the alcohol with a suitable base such as LDA followed by an acylating agent such as an acid chloride. See, e.g., U.S. Patent No. 5,399,726 which is incorporated herein by reference with respect to the preparation of taxanes having different C2 and C4 acyloxy substituents.

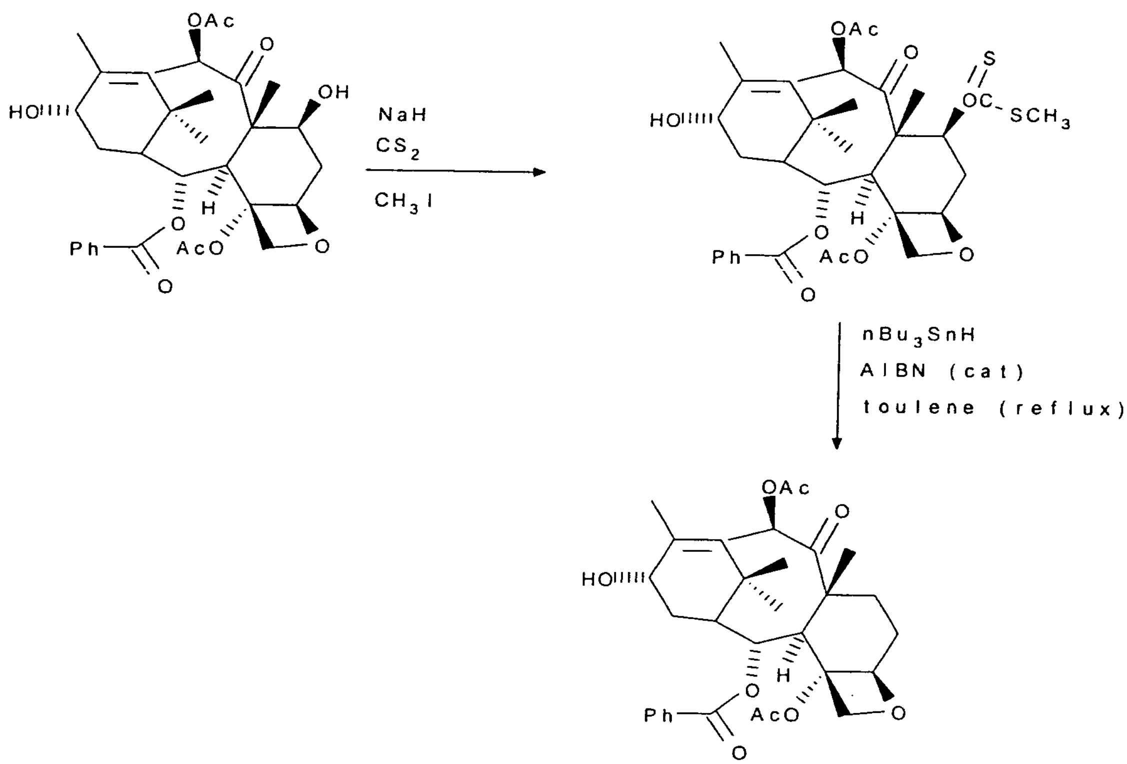
In Reaction Scheme 9, 7,10,13-protected 10-DAB **38** is converted to the diol **39** with lithium aluminum hydride. Deprotonation of diol **39** with LDA followed by reaction with an acid chloride selectively gives the C2 ester 40. Deprotonation of the C2 ester 40 with LDA followed by reaction with acid chloride gives the C2, C4 ester 41. If a chloroformate is used instead of the acid chloride, the product is a C2 or C4 carbonate ($-OCOOZ_2$ or $-OCOOZ_4$).

REACTION SCHEME 9

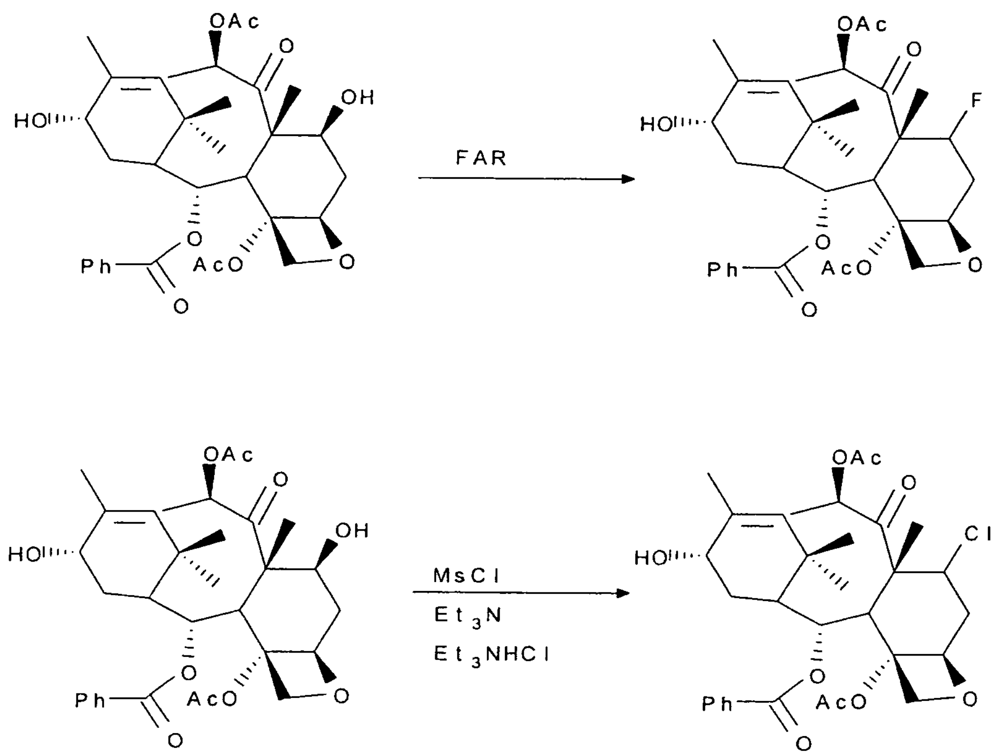


C7 dihydro and other C7 substituted taxanes can be prepared as set forth in Reaction Schemes 10, 11 and 12.

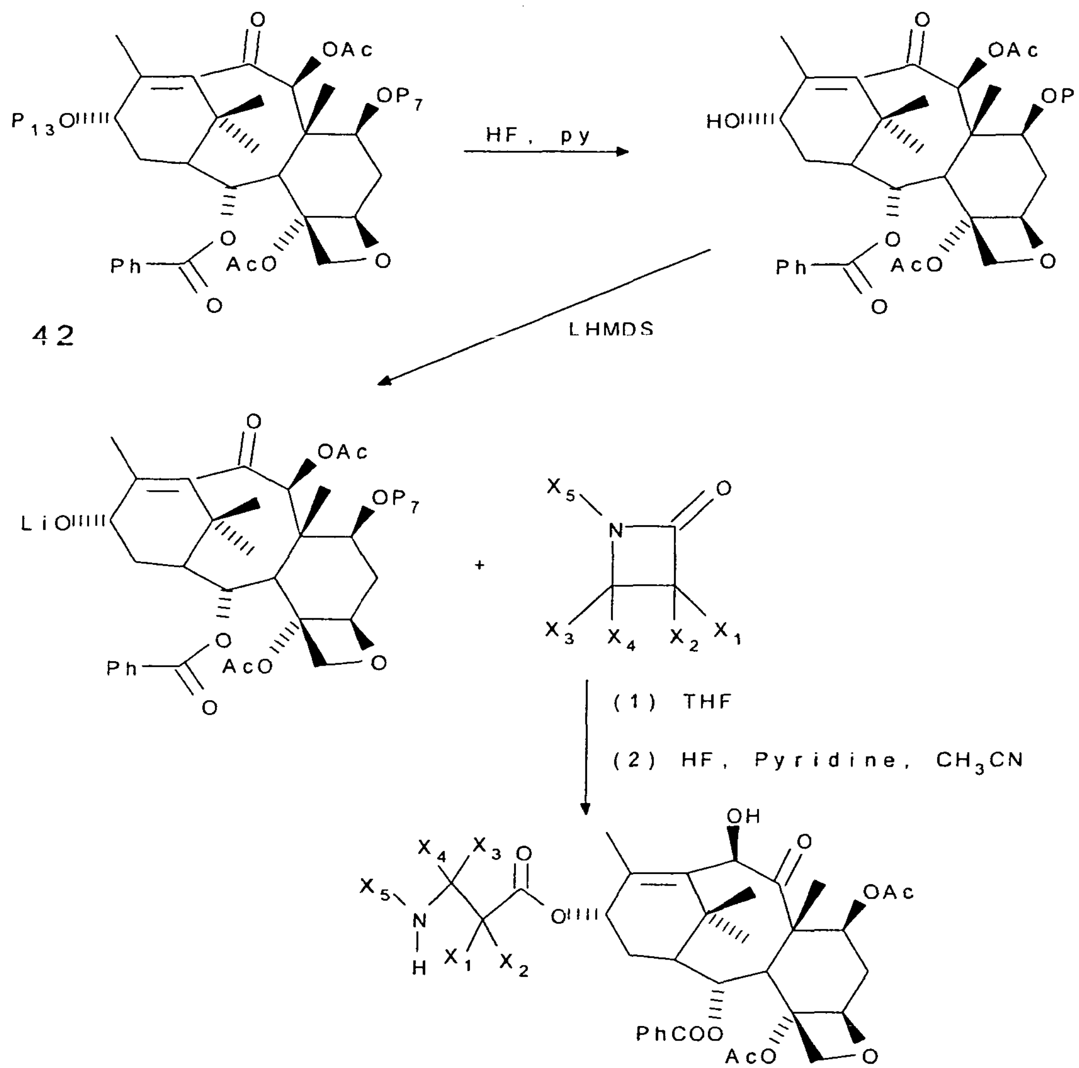
REACTION SCHEME 10



REACTION SCHEME 11



REACTION SCHEME 12



As shown in Reaction Scheme 11, 1-deoxy-baccatin III may be converted into 7-fluoro 1-deoxy-baccatin III by treatment with FAR at room temperature in THF solution. Other 1-deoxy-baccatin derivatives with a free C7 hydroxyl group behave similarly. Alternatively, 7-1-deoxy-chloro baccatin III can be prepared by treatment of baccatin III with methane sulfonyl chloride

and triethylamine in methylene chloride solution containing an excess of triethylamine hydrochloride.

Taxanes having C7 acyloxy substituents can be prepared as set forth in Reaction Scheme 12. 7,13-protected 10-oxo-derivative **42** is converted to its corresponding C13 alkoxide by selectively removing the C13 protecting group and replacing it with a metal such as lithium. The alkoxide is then reacted with a β-lactam or other side chain precursor. Subsequent hydrolysis of the C7 protecting groups causes a migration of the C7 hydroxy substituent to C10, migration of the C10 oxo substituent to C9, and migration of the C9 acyloxy substituent to C7.

1-deoxy taxanes having alternative C6 substituents can be prepared using the reactions described in Liang et al., Tetrahedron Letters, Vol. 36, No. 17, pp. 2901-2904 (1995), starting, however, with 1-deoxy-10,13-protected-10-DAB instead of taxol. According to this reaction scheme, 1-deoxy-10,13-protected-10-DAB is converted to the 7-0-triflate using CF_3SO_2Cl. Treatment of the 7-0-triflate with 1,8-diazabicyclo(5,4,0)-undec-7-ene (DBU) produces the 7-deoxy intermediate which when reacted with OsO_4 followed by an acid chloride (or chloroformate) yields the corresponding C6 ester or carbonate.

As used herein, "Ar" means aryl; "Ph" means phenyl; "Bz" means benzoyl; "Me" means methyl; "Et" means ethyl; "iPr" means isopropyl; "tBu" and "t-Bu" means tert-butyl; "R" means lower alkyl unless otherwise defined; "Ac" means acetyl; "py" means pyridine; "TES" means triethylsilyl; "TMS" means trimethyl-silyl; "TBS" means Me_2t-BuSi-; "Tf" means $-SO_2CF_3$; "BMDA" means $BrMgNiPr_2$; "Swern" means $(COCl)_2$, Et_3N; "LTMP" means lithium tetramethylpiperidide; "MOP" means 2-methoxy-2-

propyl; "BOM" means benzyloxymethyl; "LDA" means lithium diisopropylamide; "LAH" means lithium aluminum hydride; "Red-Al" means sodium bis(2-methoxyethoxy) aluminum hydride; "Ms" means CH_3SO_2-; "TASF" means tris(diethylamino)-sulfonium-difluorotrimethylsilicate; "Ts" means toluene-sulfonyl; "TBAF" means tetrabutyl ammonium hydride; "TPAP" means tetrapropyl-ammonium perruthenate; "DBU" means diazabicycloundecane; "DMAP" means p-dimethylamino pyridine; "LHMDS" means lithium hexamethyldisilazide; "DMF" means dimethylformamide; "AIBN" means azo-(bis)-isobutyronitrile; "10-DAB" means 10-desacetylbaccatin III; "FAR" means 2-chloro-1,1,2-trifluorotriethylamine; "mCPBA" means meta-chloroperbenzoic acid; "DDQ" means dicyanodichloroquinone; "sulfhydryl protecting group" includes, but is not limited to, hemithioacetals such as 1-ethoxyethyl and methoxymethyl, thioesters, or thiocarbonates; "amine protecting group" includes, but is not limited to, carbamates, for example, 2,2,2-trichloroethylcarbamate or tertbutylcarbamate; "protected hydroxy" means -OP wherein P is a hydroxy protecting group; and "hydroxy protecting group" includes, but is not limited to, acetals having two to ten carbons, ketals having two to ten carbons, ethers such as methyl, t-butyl, benzyl, p-methoxybenzyl, p-nitrobenzyl, allyl, trityl, methoxymethyl, methoxyethoxymethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrothiopyranyl, and trialkylsilyl ethers such as trimethylsilyl ether, triethylsilyl ether, dimethylarylsilyl ether, triisopropylsilyl ether and t-butyldimethylsilyl ether; esters such as benzoyl, acetyl, phenylacetyl, formyl, mono-, di-, and trihaloacetyl such as chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoro-acetyl; and carbonates

including but not limited to alkyl carbonates having from one to six carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl; isobutyl, and n-pentyl; alkyl carbonates having from one to six carbon atoms and substituted with one or more halogen atoms such as 2,2,2-trichloroethoxymethyl and 2,2,2-tri-chloroethyl; alkenyl carbonates having from two to six carbon atoms such as vinyl and allyl; cycloalkyl carbonates having from three to six carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; and phenyl or benzyl carbonates optionally substituted on the ring with one or more C_{1-6} alkoxy, or nitro. Other hydroxyl, sulfhydryl and amine protecting groups may be found in "Protective Groups in Organic Synthesis" by T. W. Greene, John Wiley and Sons, 1981.

The "hydrocarbon" moities described herein are organic compounds or radicals consisting exclusively of the elements carbon and hydrogen. These moieties include alkyl, alkenyl, alkynyl, and aryl moieties. These moieties also include alkyl, alkenyl, alkynyl, and aryl moieties substituted with other aliphatic or cyclic hydrocarbon groups, such as alkaryl, alkenaryl and alkynaryl. Preferably, these moieties comprise 1 to 20 carbon atoms.

The alkyl groups described herein are preferably lower alkyl containing from one to six carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain and include methyl, ethyl, propyl, isopropyl, butyl, hexyl and the like. They may be substituted with aliphatic or cyclic hydrocarbon radicals or hetero-substituted with the various substituents defined herein.

The alkenyl groups described herein are preferably lower alkenyl containing from two to six

carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, hexenyl, and the like. They may be substituted with aliphatic or cyclic hydrocarbon radicals or hetero-substituted with the various substituents defined herein.

The alkynyl groups described herein are preferably lower alkynyl containing from two to six carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain and include ethynyl, propynyl, butynyl, isobutynyl, hexynyl, and the like. They may be substituted with aliphatic or cyclic hydrocarbon radicals or hetero-substituted with the various substituents defined herein.

The aryl moieties described herein contain from 6 to 20 carbon atoms and include phenyl. They may be hydro-carbon or heterosubstituted with the various substituents defined herein. Phenyl is the more preferred aryl.

The heteroaryl moieties described are heterocyclic compounds or radicals which are analogous to aromatic compounds or radicals and which contain a total of 5 to 20 atoms, usually 5 or 6 ring atoms, and at least one atom other than carbon, such as furyl, thienyl, pyridyl and the like. The heteroaryl moieties may be substituted with hydrocarbon, heterosubstituted hydrocarbon or hetero-atom containing substituents with the hetero-atoms being selected from the group consisting of nitrogen, oxygen, silicon, phosphorous, boron, sulfur, and halogens. These substituents include lower alkoxy such as methoxy, ethoxy, butoxy; halogen such as chloro or fluoro; ethers; acetals; ketals; esters; heteroaryl

such as furyl or thienyl; alkanoxy; hydroxy; protected hydroxy; acyl; acyloxy; nitro; amino; and amido.

The heterosubstituted hydrocarbon moieties described herein are hydrocarbon moieties which are substituted with at least one atom other than carbon, including moieties in which a carbon chain atom is substituted with a hetero atom such as nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or a halogen atom. These substituents include lower alkoxy such as methoxy, ethoxy, butoxy; halogen such as chloro or fluoro; ethers; acetals; ketals; esters; heteroaryl such as furyl or thienyl; alkanoxy; hydroxy; protected hydroxy; acyl; acyloxy; nitro; amino; and amido.

The acyl moieties described herein contain hydrocarbon, substituted hydrocarbon or heteroaryl moieties.

The alkoxycarbonyloxy moieties described herein comprise lower hydrocarbon or substituted hydrocarbon moieties.

The following examples illustrate the invention.

EXAMPLE

REACTION SCHEME 1

Hydroxyketone **2**. To a stirred solution of 3,10-diol **1** (3.49 g, 14.78 mmol) in 35 mL of DMF under nitrogen at 0 °C was added pyridinium dichromate ("PDC") (7.20 g, 19.15 mmol) as a solid in three portions over a 30 min. period. The reaction mixture was then warmed to room temperature. After 6 h, the reaction mixture was poured into 500 mL of H_2O and extracted with three 200 mL portions of 15% ethyl acetate in hexane. The organic layers were combined and dried over anhydrous Na_2SO_4. Removal of the solvent followed by flash chromatography

purification (10% EtOAc/hexane) gave 3.34 g (97% yield) of the desired hydroxyketone **2** as a white solid.

2: mp: 73-74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.96 (s, 3H, Me16), 1.06 (s, 3H, Me17), 1.20 (d, J = 7.1 Hz, 3H, Me19), 1.38 (d, J = 14.8 Hz, 1H, H2α), 1.70 (d, J = 1.7 Hz, 3H, Me18), 1.76 (t, J = 6.0 Hz, 1H, H1), 2.00 (br d, J = 18.1 Hz, 1H, H14α), 2.07 (dd, J = 19.2, 7.7 Hz, 1H, H9β), 2.45 (br d, J = 18.1 Hz, 1H, H14β), 2.61 (ddq, J = 11.5, 7.7, 7.1 Hz, 1H, H8α), 2.66 (dd, J = 14.8, 6.0 Hz, 1H, H2β), 2.72 (dd, J = 19.2, 11.5 Hz, 1H9α), 2.81 (s, 1H, OH3), 5.43 (m, 1H, H13); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 16.40, 21.44, 21.75, 25.46, 33.48, 38.29, 44.68, 44.77, 47.06, 48.41, 73.07, 94.19, 121.72, 138.34, 217.54; IR (CCl_4) υ 3520, 3000, 2960, 2900, 2820, 1730, 1440, 1330, 990, 970 cm^{-1}; MS (CI) 235 (M^{+}+1, 100), 217 (65).

Triethylsilyl enol ether **3**. To a stirred 0.94 M solution of LDA in THF (1.41 mL, 1.33 mmol) under nitrogen at -78 °C was added a solution of hydroxyketone **2** (156 mg, 0.667 mmol) in 1.5 mL of THF and 0.23 mL of HMPA (1.33 mmol) dropwise down the side of the flask. After 0.5 h, a 0.1 M solution (6.67 mL, 0.667 mmol) of TESCl in THF was added down the side of the flask at a rate of 0.1 mL/min. After the addition was complete, the reaction mixture was stirred for an additional 5 min. and then rapidly poured into 50 mL of a vigorously stirred saturated aqueous $NaHCO_3$ solution. The mixture was extracted with three 50 mL portions of hexane and the combined organic layers were washed with 20 mL of H_2O, dried over anhydrous Na_2SO_4. Removal of the solvent followed by flash chromatography purification (10% EtOAc/hexane) gave 225 mg of triethylsilyl enol ether **3** (97% yield) as a colorless oil.

3: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.71 (q, J = 7.7 Hz, 6H, TES CH_2), 0.89 (s, 3H, Me16), 0.98 (t, J = 7.7 Hz, 9H, TES CH_3), 1.06 (d, J = 7.1 Hz, 3H, Me19), 1.13 (s, 3H, Me17), 1.28 (d, J = 14.3 Hz, 1H, H2α), 1.66 (dd, J = 6.0, 5.5 Hz, 1H, H1), 1.76 (dd, J = 2.2, 1.7 Hz, 3H, Me18), 1.95 (br d, J = 18.7 Hz, 1H, H14α), 2.33 (ddd, J =14.3, 6.0, 2.2 Hz, 1H, H2β), 2.42 (br d, J = 18.7 Hz, 1H, H14β), 2.72 (qd, J = 7.7, 2.1 Hz, 1H, H8α), 3.08 (s, 1H, OH3), 4.45 (d, J = 2.1 Hz, 1H, H9), 5.50 (m, 1H, H13); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 4.51, 6.46, 16.10, 21.58, 22.76, 25.10, 33.57, 43.78, 44.11, 45.13, 45.16, 71.32, 91.75, 106.27, 120.82, 140.25, 151.77; IR (CCl_4) υ 3510, 3010, 2960, 2910, 2880, 2830, 1630, 1440, 1330, 1310, 1230, 1150, 1040, 1010, 880, 700 cm^{-1}; MS (CI) 349 (M^++1, 54), 331 (100).

Triethylsilyloxy ketone **4**. To a stirred solution of triethylsilyl enol ether **3** (5.335 g, 15.33 mmol) in 300 mL of hexane under nitrogen at 0 °C was added 6.427 g of $NaHCO_3$ (76.55 mmol) and 4.533 g of *m*-chloroperoxybenzoic acid (67% purity, 17.60 mmol) in four portions over a 0.5 h period. After 2.5 h, the reaction mixture was diluted with 200 mL of hexane and poured into 400 mL of a 1:1 mixture of a saturated aqueous $NaHCO_3$ solution and a saturated aqueous $Na_2S_2O_3$ solution. The organic layer was separated, and the aqueous layer was extracted with two 100 mL portions of hexane. The combined organic layers were washed with 100 mL of H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 5.7 g of a yellowish oil. This material was purified by flash chromatography (5% EtOAc/hexane) to give 5.495 g of triethylsilyloxy ketone **4** (98% yield) as a colorless oil.

4: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.65 (q, J = 7.7 Hz, 6H, TES CH_2), 0.90 (s, 3H, Me16), 0.97 (t, J = 7.7 Hz, 9H, TES CH_3), 1.06 (s, 3H, Me17), 1.11 (d, J = 7.7 Hz, 3H, Me19), 1.39 (d, J = 14.8 Hz, 1H, H2α), 1.76 (d, J = 1.7 Hz, 3H, Me18), 1.76 (dd, J = 6.1, 5.5 Hz, 1H, H1), 2.17 (br d, J = 18.7 Hz, 1H, H14α), 2.33 (dq, J = 9.3, 7.7 Hz, 1H, H8α), 2.46 (br d, J = 18.7 Hz, 1H, H14β), 2.64 (ddd, J = 14.8, 6.1, 2.2 Hz, 1H, H2β), 2.79 (br s, 1H, OH3), 3.85 (d, J = 9.3 Hz, 1H, H9), 5.54 (m, 1H, H13); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 4.90, 6.48, 13.98, 21.47, 21.94 26.94, 33.42, 44.33, 44.49, 46.79, 48.59, 70.51, 83.33, 90.04, 121.71, 138.66, 214.42; IR (CCl_4) υ 3520, 3000, 2960, 2920, 2880, 2830, 1730, 1450, 1330, 1220, 1160, 1105, 980, 960, 920, 700 cm^{-1}; MS (CI) 365 (M^++1, 34), 347 (100), 335 (42), 233 (35).

Triethylsilyloxy diol **5**. To a stirred suspension of 0.263 g (6.932 mmol) of lithium aluminum hydride in 30 mL of ethyl ether under nitrogen at 0 °C was added a solution of 2.527 g (6.932 mmol) of triethylsilyloxy ketone **4** in 20 mL of ethyl ether. The reaction mixture was warmed to room temperature. After 2 h at room temperature, the mixture was recooled to 0 °C, diluted with 50 mL of ethyl ether, and quenched by dropwise addition of 2.5 mL of H_2O. After stirring another 2 h at room temperature, the white suspension was further diluted with 100 mL of ethyl acetate, dried over anhydrous Na_2SO_4, and filtered through a 0.5 inch pad of celite. The filtrate was concentrated under reduced pressure to give 2.434 g of triethylsilyloxy diol **5** (96% yield) as a white solid, which was used without any further purification.

5: mp: 62-63 °C; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.62 (q, J = 7.7 Hz, 6H, TES CH_2), 0.97 (t, J = 7.7

Hz, 9H, TES CH_3), 1.08 (s, 3H, Me16), 1.09 (d, J = 7.1 Hz, 3H, Me19), 1.18 (d, J = 14.8 Hz, 1H, H2α), 1.20 (s, 3H, Me17), 1.48 (dd, J =6.6, 6.1 Hz, 1H, H1), 1.84 (d, J = 1.7 Hz, 3H, Me18), 1.97 (dq, J = 8.8, 7.1 Hz, 1H, H8α), 2.17 (br d, J = 18.7 Hz, 1H, H14α), 2.43 (br d, J = 18.7 Hz, 1H, H14β), 2.47 (ddd, J = 14.8, 6.1, 2.2 Hz, 1H, H2β), 2.74 (br s, 1H, OH3), 4.01 (dd, J = 8.8, 8.2 Hz, 1H, H9β), 4.28 (d, J = 8.2 Hz, 1H, H10), 5.55 (m, 1H, H13); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 5.16, 6.60, 12.82, 21.96, 23.63, 27.76, 33.88, 44.16, 44.96, 45.31, 48.27, 63.33, 81.46, 83.37, 122.03, 141.62; IR (CCl_4) υ 3640, 3550, 3020, 2970, 2920, 2890, 2850, 1450, 1330, 1240, 1160, 1140, 1120, 1100, 1080, 1040, 1000, 970, 960, 860, 840, 710 cm^{-1}; MS (CI) 367 (M^{+}+1, 21), 349 (100), 337 (22), 319 (42).

Triethylsilyloxy keto diol **6**. To a vigorously stirred solution of triethylsilyloxy diol **5** (886 mg, 2.42 mmol) in 25 mL of CH_2Cl_2 at 0 °C under nitrogen was added 1.08 mL (3.63 mmol) of $Ti(Oi\text{-}Pr)_4$ followed by dropwise addition of 1.82 mL (3.63 mmol) of a 2 M solution of *t*-BuOOH in hexane. After an additional 2 h, 2.5 mL of dimethyl-sulfide was added and the reaction mixture was warmed in a 42 °C bath to reflux for 12 h. The solvent was evaporated under reduced pressure. The residue was dissolved in 200 mL of THF at room temperature and 0.5 mL of H_2O was added dropwise with vigorously stirring. After 2 h, the resulting white suspension was dried over anhydrous Na_2SO_4, and then filtered through a 0.5 inch pad of celite, eluting with two 50 mL portions of ethyl acetate. The filtrate was concentrated under reduced pressure to afford a yellow oil. This oil was purified by flash chromatography (10% EtOAc/hexane) to give 866.7

mg of triethylsilyloxy keto diol **6** (94% yield) as a white solid.

6: mp 106-107 °C; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.71 (q, J = 7.7 Hz, 6H, TES CH_2), 1.01 (t, J = 7.7 Hz, 9H, TES CH_3), 1.01 (s, 3H, Me17), 1.07 (d, J = 7.1 Hz, 3H, Me19), 1.53 (s, 3H, Me16), 1.73 (s, 3H, Me18), 1.80-1.94 (m, 3H, H1, H2β, H14α), 2.02 (d, J = 3.3 Hz, 1H, OH10), 2.22 (dq, J =9.9, 7.1 Hz, 1H, H8α), 2.52 (d, J = 12.1 Hz, 1H, OH13), 2.81 (dd, J = 11.5, 3.3 Hz, 1H, H2α) 2.83 (m, 1H, H14β), 4.08 (br t, J = 11.5 Hz, 1H, H13), 4.16 (dd, J =9.9, 8.8 Hz, 1H, H9), 4.56 (dd, J = 8.8, 3.3 Hz, 1H, H10); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 5.36, 6.72, 15.84, 17.96, 26.11, 29.30 34.83, 38.44, 41.00, 45.98, 54.49, 66.94, 77.15, 77.21, 137.66, 140.65, 215.86; IR (CCl_4) υ 3650, 3550, 3460, 2980, 2900, 2870, 1670, 1455, 1410, 1370, 1280, 1240, 1210, 1160, 1090, 1050, 1030, 1010, 960, 860, 720 cm^{-1}; MS (EI) 382 (M^+, 2), 353 (10), 335 (5), 307 (4), 250 (4), 215 (67), 75 (100).

t-Butyldimethylsilyloxy ketone **7**. To a stirred solution of triethylsilyloxy keto diol **6** (883 mg, 2.31 mmol) in 35 mL of pyridine under nitrogen at 0 °C was added dropwise 0.485 mL(2.771 mmol) of TBSOTf. The solution was then warmed to room temperature. After 2 h at room temperature, the solution was diluted with 100 mL of hexane and poured into 150 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with two 100 mL portions of hexane. The organic layers were combined, and washed with 50 mL of a 10% aqueous $CuSO_4$ solution followed by 20 mL of H_2O, and dried over anhydrous Na_2SO_4. Removal of the solvent followed by flash chromatography purification (2.5% EtOAc/hexane) to give 1.122 g of

t-butyldimethylsilyloxy ketone **7** (98% yield) as a white solid.

7: mp: 128 -130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.04 (s, 3H, TBS CH_3), 0.06 (s, 3H, TBS CH_3), 0.63 q, J = 7.7 Hz, 6H, TES CH_2), 0.93 (s, 9H, TBS t-Bu), 1.01 (t, J = 7.7 Hz, 9H, TES CH_3), 1.06 (d, J = 7.1 Hz, 3H, Me19), 1.09 (s, 3H, Me17), 1.56 (s, 3H, Me16), 1.66 (d, J = 1.1 Hz, 3H, Me18), 1.82 (m, 1H, H1), 1.85 (m, 1H, H2β), 1.90 (d, J = 3.3 Hz, 1H, OH10), 1.93 (dd, J = 14.3, 5.5 Hz, 1H, H14α), 2.16 (dq, J = 10.4, 7.1 Hz, 1H, H8α), 2.49 (ddd, J = 14.3, 7.8, 2.2 Hz, 1H, H14β), 2.72 (dd, J = 12.1, 2.7 Hz, 1H, H2α), 4.19 (dd, J = 10.4, 8.8 Hz, 1H, H9), 4.46 (ddd, J = 7.8, 5.5, 1.1, 1H, H13), 4.58 (dd, J = 8.8, 3.3 Hz, 1H, H10); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) -5.48, -4.54, 5.33, 6.68, 15.30, 16.42, 17.77, 25.65, 27.15, 27.38, 33.93 38.94, 41.26, 45.83, 53.87, 67.27, 77.23, 77.61, 135.08, 142.06, 209.77; IR (CCl_4) υ 3530, 2950, 2930, 2870, 1670, 1460, 1250, 1090, 1030, 1010, 970, 910, 870, 830, 770, 740 cm^{-1}; MS (CI) 497 (M$^+$+1, 16), 479 (100), 365 (28), 346 (35), 307 (22), 205 (91).

Trimethylsilyl enol ether **8**. To a stirred solution of t-butyldimethylsilyloxy ketone **7** (287 mg, 0.55 mmol) in 2.5 mL of THF and 0.3 mL of HMPA (3.3 mmol) under nitrogen at room temperature, was added dropwise a solution of 0.44 M LDA in THF (3.8 mL, 1.65 mmol). After stirring at room temperature for 10 min., a 1.0 M solution of TMSCl (1.7 mL, 1.65 mmol) in THF was added dropwise at a rate of 0.1 mL/min. After the addition was complete, the reaction was stirred for another 2 minutes. Then 2.5 mL of triethylamine was added and the reaction mixture was poured into 150 mL of a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with three 50 mL portions of hexane. The combined organic

layers were washed with 50 mL of H_2O, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 370 mg of trimethylsilyl enol ether **8** (99% yield) as a colorless oil. This material was used in the next step without further purification.

8: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 0.08 (s, 3H, TBS CH_3), 0.11 (s, 3H, TBS CH_3), 0.14 (s, 9H, TMS CH_3), 0.16 (s, 9H, enol TMS CH_3), 0.63 (q, J = 7.5 Hz, 6H, TES CH_2), 0.81 (d, J = 7.0 Hz, 3H, Me19), 0.92 (s, 9H, TBS *t*-Bu), 0.98 (t, J = 7.5 Hz, 9H, TES CH_3), 1.09 (s, 3H, Me17), 1.23 (ddd, J =14.0, 10.5, 5.5 Hz, 1H, H14α), 1.24 (s, 3H, Me16), 1.81 (d, J = 1.5 Hz, 3H, Me18), 1.96 (ddd, J = 10.5, 8.5, 5.5 Hz, 1H, H1), 2.30 (dq, J = 7.0, 7.0 Hz, 1H, H8α), 2.51 (ddd, J = 14.0, 10.5, 7.5 Hz, 1H, H14β), 3.77 (dd, J = 7.0, 6.4 Hz, 1H, H9), 4.63 (d, J = 6.4 Hz, 1H, H10), 4.67 (ddd, J = 10.5, 7.5, 1.5 Hz, 1H, H13), 4.95 (d, J = 8.5 Hz, 1H, H2); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) -5.27, -4.71, 1.06, 0.53, 4.96, 6.86, 12.94, 15.72, 18.11, 25.77, 28.76, 32.02, 37.54, 40.70, 41.79, 41.90, 69.53, 78.61, 80.96, 112.22, 139.48, 139.87, 155.26; IR ($CHCl_3$) υ 2960, 2880, 2870, 1680, 1630, 1460, 1250, 1130, 1080, 1000, 900, 880, 830 cm^{-1}; MS (CI) 641 (M^++1, 9), 551 (65), 508 (100), 379 (80).

Hydroxy ketone **9**. To a stirred solution of 321 mg (0.501 mmol) of trimethylsilyl enol ether **8** in 15 mL of THF under nitrogen at 0 °C was added 216 mg (80% pure, 1.00 mmol) of *m*-chloroperoxybenzoic acid as a solid in three portions. After 3 h, the reaction mixture was diluted with 50 mL of hexane and poured into 200 mL of a 1:1 mixture of a saturated aqueous $NaHCO_3$ solution and a saturated aqueous $Na_2S_2O_3$ solution. The organic layer was separated, and the aqueous layer was extracted with three 100 mL portions of hexane. The combined organic layers

were washed with 100 mL of H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 332 mg of the corresponding trimethyl-silyloxy epoxide as a white solid. This material was used in the next step without further purification.

A solution of 332 mg of the above trimethylsilyloxy epoxide (ca. 0.501 mmol) in 5 mL of methanol and 0.5 mL of $CHCl_3$ was stirred at room temperature for 24 h. Removal of the solvent followed by flash chromatography purification (5% EtOAc/hexane) gave 266 mg of hydroxy ketone **9** as a white solid (91% yield from trimethylsilyl enol ether **8**).

9: mp: 111-112 °C; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.04 (s, 3H, TBS CH_3), 0.07 (s, 3H, TBS CH_3), 0.18 (s, 9H, TMS CH_3), 0.62 (q, J = 7.7 Hz, 6H, TES CH_2), 0.93 (s, 9H, TBS *t*-Bu), 0.97 (t, J = 7.7 Hz, 9H, TES CH_3), 1.06 (d, J = 7.1 Hz, 3H, Me19), 1.08 (s, 3H, Me17), 1.35 (s, 3H, Me16), 1.65 (s, 3H, Me18), 1.81 (dd, J = 14.8, 4.4 Hz, 1H, H14α), 1.95 (dd, J = 7.7, 3.8 Hz, 1H, H1), 2.26 (ddd, J = 14.8, 10.4, 7.7 Hz, 1H, H14β), 2.30 (dq, J = 10.4, 7.1 Hz, 1H, H8α), 3.30 (d, J = 8.3 Hz, 1H, OH2), 4.22 (dd, J = 10.4, 8.8 Hz, 1H, H9), 4.35 (br dd, J = 10.4, 4.4 Hz, 1H, H13), 4.41 (dd, J = 8.3, 3.8 Hz, 1H, H2), 4.54 (d, J = 8.8 Hz, 1H, H10); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) -5.44, -4.52, 0.95, 4.85, 6.81, 15.46, 17.62, 17.83, 25.65, 26.22, 28.21, 28.39, 36.69, 52.19, 54.33, 66.94, 71.25, 75.74, 77.43, 137.10, 140.25, 211.59; IR (CCl_4) υ 3530, 2960, 2890, 2870, 1680, 1460, 1240, 1160, 1120, 1080, 1060, 1020, 1000, 990, 880, 830 cm^{-1}; MS (CI) 585 (M^{+}+1, 34), 584 (69), 567 (13), 453 (100), 363 (30), 323 (52).

Triol **10**. To a solution of 4-bromo-4-penten-1-ol (770.0 mg, 4.7 mmol) in 20 mL of Et_2O at -78 °C under

N_2 was added a 1.7 M solution of t-BuLi (8 mL, 13.6 mmol) in hexane. The solution was then stirred at 0 °C for 2 h. After cooling to -10 °C, a solution of hydroxy ketone **9** (370 mg, 0.63 mmol) in 5 mL of Et_2O was added. The solution was stirred at -10 °C for 0.5 h, and then poured into 150 mL of a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (100 mL, 3 times). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (20% EtOAc/hexane) to give 400 mg (95% yield) of the desired triol **10** as a colorless oil.

10: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.136 (s, 12H, TMS CH_3, TBS CH_3), 0.159 (s, 3H, TBS CH_3), 0.669 (qd, J=8.0, 1.5 Hz, 6H, TES CH_2), 0.770 (d, J=7.0 Hz, 3H, Me19), 0.921 (s, 9H, TBS *t*-Bu), 0.991 (t, J=8.0 Hz, 9H, TES CH_3), 1.038 (s, 3H, Me17), 1.488 (s, 3H, Me16), 1.702 (t, J=6.0 Hz, 1H, OH7), 1.729 (s, 3H, Me18), 1.779-1.830 (m, 3H, 2xH6, H8), 1.869 (dd, J=9.0, 2.8 Hz, 1H, H1), 2.101 (m, 2H, 2xH5), 2.134 (d, J=16.0 Hz, 1H, H14α), 2.545 (dt, J=16.0, 9.0 Hz, 1H, H14β), 2.905 (br, 1H, OH2), 3.473 (s, 1H, OH3), 3.670-3.726 (m, 2H, 2xH7), 4.060 (m, 1H, H2β), 4.070 (dd, J=8.0, 6.5 Hz, 1H, H9β), 4.250 (d, J=8.0 Hz, 1H, H10α), 4.322 (d, J=9.0 Hz, 1H, H13β), 4.968 (s, 1H, 1xH20), 5.190 (s, 1H, 1xH20); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) -5.19, -4.57, 0.89, 5.05, 6.83, 13.10, 17.74, 19.33, 25.54, 26.18, 28.64, 29.94, 30.97, 34.40, 35.78, 45.27, 51.44, 62.31, 68.88, 73.80, 79.87, 83.83, 109.95, 135.03, 142.32; IR ($CHCl_3$): υ 2950, 2870, 1090, 1060, 980, 890 cm^{-1}; MS (CI): 653 (M^++1-H_2O), 539, 521, 503, 449, 431, 407, 390, 316, 294, 244.

Carbonate **11**. To a solution of triol **10** (405 mg, 0.60 mmol) in 20 mL of CH_2Cl_2 at -78 °C under N_2 was

added 4.7 mL (60.0 mmol) of pyridine, followed by a solution of $COCl_2$ (6.0 mL, 6.0 mmol) in toluene. The mixture was then warmed to 0 °C and stirred at that temperature for 50 minutes. Then the mixture was diluted with 100 mL of EtOAc and poured into 200 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and aqueous layer was extracted with EtOAc (100 mL, 3 times). The organic layers were combined and dried over Na_2SO_4. Removal of the solvent gave the desired carbonate **11** a pale yellow oil, which was used without further purification.

11: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.085 (s, 3H, TBS CH_3), 0.100 (s, 12H, TBS CH_3, TMS CH_3), 0.652 (qd, J=7.5, 1.5 Hz, 6H, TES CH_2), 0.912 (s, 9H, TBS *t*-Bu), 0.950 (d, J=6.0 Hz, 3H, Me19), 0.984 (t, J=7.5 Hz, 9H, TES CH_3), 1.199 (s, 3H, Me17), 1.434 (ddd, J=18.5, 9.0, 4.5 Hz, 1H, H14α), 1.481 (s, 3H, Me16), 1.637 (m, 1H, 1xH6), 1.722 (m, 1H, 1xH6), 1.786 (d, J=1.0 Hz, 3H, Me18), 2.192-2.349 (m, 4H, 2xH5, H1, H14β), 2.396 (qd, J=6.0, 5.0 Hz, 1H, H8), 3.658 (qd, J=6.5, 3.0 Hz, 2H, 2xH7), 3.982 (dd, J=8.0, 5.0 Hz, 1H, H9β), 4.509 (d, J=8.0 Hz, 1H, H10α), 4.771 (td, J=9.0, 1.0 Hz, 1H, H13β), 4.858 (d, J=4.0 Hz, 1H, H2), 5.275 (s, 2H, 2xH20).

Acetate **12**. To a solution of the above carbonate **11** in 5 mL of pyridine at room temperature under N_2 was added Ac_2O (0.6 mL, 6.3 mmol). After stirring at room temperature for 9 h, the solution was diluted with 100 mL of 20% EtOAc in hexane, and poured into 100 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with 20% EtOAc in hexane (100 mL, 3 times). The organic layers were combined and dried over Na_2SO_4. Removal of the solvent followed by flash chromatography

purification (8% EtOAc/hexane) gave 433.2 mg (98% yield) of the desired acetate **12** as a colorless oil.

12: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.085 (s, 3H, TBS CH_3), 0.097 (s, 12H, TMS CH_3, TBS CH_3), 0.654 (qd, J=8.0, 2.0 Hz, 6H, TES CH_2), 0.913 (s, 9H, TBS *t*-Bu), 0.935 (d, J=7.5 Hz, 3H, Me19), 0.985 (t, J=8.0 Hz, 9H, TES CH_3), 1.201 (s, 3H, Me17), 1.429 (m, 1H, H14α), 1.480 (s, 3H, Me16), 1.711 (m, 1H, 1xH6), 1.788 (s, 3H, Me18), 1.820 (m, 1H, 1xH6), 2.041 (s, 3H, $COCH_3$), 2.153-2.351 (m, 4H, H1, 2xH5, H14β), 2.403 (dq, J=8.0, 7.5 Hz, 1H, H8), 3.977 (dd, J=8.0, 5.5 Hz, 1H, H9β), 4.075 (t, J=6.5 Hz, 2H, 2xH7), 4.510 (d, J=8.0 Hz, 1H, H10α), 4.771 (t, J=8.0 Hz, 1H, H13β), 4.835 (d, J=4.0 Hz, 1H, H2β), 5.253 (s, 1H, 1xH20), 5.286 (s, 1H, 1xH20); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) -5.37, -4.74, 0.79, 4.98, 6.74, 12.93, 15.61, 17.92, 20.53, 25.63, 27.36, 28.27, 29.77, 32.34, 32.98, 36.48, 39.11, 48.96, 63.55, 68.84, 73.02, 79.66, 88.61, 92.86, 114.68, 137.48, 141.39, 150.56, 154.08, 171.14; IR ($CHCl_3$): υ 2950, 2850, 1790, 1713, 1020, 880, 815 cm^{-1}; MS (CI): 739 (M^++1), 691, 665, 607, 563, 503, 473, 431.

Hydroxy alkene **13**. To a solution of acetate **12** (433.0 mg, 0.586 mmol) in 2 mL of CH_3CN at 0 °C was added 5.0 mL of a solution of 48% HF/pyridine/CH_3CN (1:8:8). After stirring at 0 °C for 3 h, the solution was diluted with 50 mL of EtOAc and poured into 100 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (100 mL, 3 times). The organic layers were combined and dried over Na_2SO_4. Removal of the solvent gave a pale yellow oil, which was used without further purification

To a solution of the above oil in 4 mL of CH_2Cl_2 at room temperature under N_2 was added Et_3N (0.32 mL, 2.3 mmol), followed by TESCl (0.20 mL, 1.2 mmol). After

stirring at room temperature for 1.5 h, the solution was diluted with 100 mL of 20% EtOAc in hexane, and poured into 100 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with 20% EtOAc in hexane (100 mL, 3 times). The organic layers were combined and dried over Na_2SO_4. Removal of the solvent followed by flash chromatography purification (15% EtOAc/ hexane) gave 351.0 mg of the desired hydroxy alkene **13** (90% yield) as a colorless oil, plus 2.3% starting material **12** and 1.1% 9,10-diol.

13: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.090 (s, 3H, TBS CH_3), 0.104 (s, 3H, TBS CH_3), 0.662 (qd, J=8.0, 1.5 Hz, 6H, TES CH_2), 0.915 (s, 9H, TBS *t*-Bu), 0.965 (d, J=7.5 Hz, 3H, Me19), 0.989 (t, J=8.0 Hz, 9H, TES CH_3), 1.197 (s, 3H, Me17), 1.486 (s, 3H, Me16), 1.434 (dd, J=9.5, 4.7 Hz, 1H, H14α), 1.780 (m, 1H, 1xH6), 1.810 (d, J=1.5 Hz, 3H, Me18), 1.942 (m, 1H, 1xH6), 2.045 (s, 3H, $COCH_3$), 2.191 (m, 1H, 1xH5), 2.208 (d, J=2.5 Hz, 1H, OH9), 2.262-2.333 (m, 3H, 1xH5, H1, H8), 2.360 (m, 1H, H14β), 3.986 (m, 1H, H9β), 4.112 (td, J=6.5, 2.5 Hz, 2H, 2xH7), 4.512 (d, J=8.5 Hz, 1H, H10α), 4.760-4.791 (m, 2H, H13β, H2), 5.201 (s, 1H, 1xH20), 5.320 (s, 1H, 1xH20); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) -5.41, -4.72, 4.64, 5.49, 11.23, 15.89, 17.88, 20.52, 25.60, 27.13, 27.44, 28.09, 32.49, 33.16, 36.72, 36.83, 49.11, 63.52, 68.78, 70.99, 79.13, 86.15, 92.71, 114.00, 136.37, 141.98, 147.57, 154.21, 171.20; IR ($CHCl_3$): υ 2960, 2780, 1795, 1735, 1000, 865 cm^{-1}; MS (CI): 667 (M^++1), 649, 623, 605, 587, 535, 473.

Ketone **14**. To a mixture of hydroxy alkene **13** (343.0 mg, 0.515 mmol) and 200 mg of 3A° molecular sieves in 5 mL of CH_2Cl_2 at room temperature under N_2 was added 4-methyl- morpholine (180 mg, 1.54 mmol) followed by tetra-propylammonium perruthenate (18 mg, 0.05 mmol).

After stirring at room temperature for 2 h, the mixture was filtered through a short pad of silica gel. The silica gel was washed with 200 mL of 15% EtOAc in hexane. Removal of the solvent gave 338.5 mg of the desired ketone **14** (99% yield) as a colorless oil, which was used without any further purification.

14: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.116 (s, 3H, TBS CH_3), 0.132 (s, 3H, TBS CH_3), 0.635 (qd, J=7.5, 4.0 Hz, 6H, TES CH_2), 0.936 (s, 9H, TBS *t*-Bu), 0.961 (t, J=7.5 Hz, 9H, TES CH_3), 1.051 (d, J=7.0 Hz, 3H, Me19), 1.203 (s, 3H, Me17), 1.232 (s, 3H, Me16), 1.534 (m, 1H, H14α), 1.807 (m, 1H, 1xH6), 1.885-1.981 (m, 2H, 1xH5, 1xH6), 1.942 (d, J=1.5 Hz, 3H, Me18), 2.059 (s, 3H, $COCH_3$), 2.242 (ddd, J=15.5, 10.5, 4.0 Hz, 1H, 1xH5), 2.333-2.418 (m, 2H, H14β, H1), 3.523 (q, J=7.0 Hz, 1H, H8), 4.103 (t, J=6.0 Hz, 2H, 2xH7), 4.773 (d, J=4.5 Hz, 1H, H2β), 4.868 (m, 1H, H13β), 4.935 (s, 1H, H10α), 5.282 (s, 1H, 1xH20), 5.320 (s, 1H, 1xH20); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) -5.44, -4.78, 4.60, 6.34, 15.11, 15.54, 17.91, 20.53, 25.60, 25.68, 27.01, 28.00, 32.35, 32.88, 36.69, 42.40, 47.82, 63.46, 68.70, 79.56, 85.00, 90.58, 115.91, 134.62, 143.46, 145.91, 153.47, 171.15, 209.74; IR ($CHCl_3$): υ 2960, 2880, 1800, 1750, 1000, 865 cm^{-1}; MS (CI): 665 (M^++1), 648, 637, 621, 533, 489.

Hydroxy ketone **15**. To a 0.1 M solution of $Pd(acac)_2$/n-Bu_3P (1:1) in DMF (1 mL, 0.1 mmol) at room temperature under N_2 was added a 2.37 M solution of $HCOOH/Et_3N$ (1:1) in DMF (10.2 mL, 24.2 mmol), followed by a solution of ketone **14** (320.0 mg, 0.48 mmol) in 5 mL of DMF. After stirring at room temperature for 19 h, the solution was diluted with 100 mL of Et_2O and poured into 100 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted

with Et_2O (100 mL, 3 times). The organic layers were combined and dried over Na_2SO_4. Removal of the solvent followed by flash chromatography purification (15% EtOAc/hexane) gave 280.5 mg (94% yield) of the desired hydroxy ketone **15** as a colorless oil.

15: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.138 (s, 3H, TBS CH_3), 0.149 (s, 3H, TBS CH_3), 0.628 (qd, J=7.5, 3.0 Hz, 6H, TES CH_2), 0.892 (d, J=7.0 Hz, 3H, Me19), 0.953 (s, 9H, TBS *t*-Bu), 0.962 (t, J=7.5 Hz, 9H, TES CH_3), 1.104 (s, 3H, Me17), 1.201 (s, 3H, Me16), 1.409 (ddd, J=14.5, 4.5, 4.0 Hz, 1H, H14α), 1.464 (q, J=6.0 Hz, 1H, 1xH5), 1.783 (br, 1H, OH2), 1.805-1.863 (m, 2H, 2xH6), 1.910 (d, J=1.0 Hz, 3H, Me18), 2.054 (m, 1H, H1), 2.063 (s, 3H, $COCH_3$), 2.367-2.473 (m, 3H, H14β, 1xH5, H3), 3.024 (dq, J=9.0, 7.0 Hz, 1H, H8), 3.880 (ddd, J=9.5, 2.5, 2.0 Hz, 1H, H2β), 4.102 (m, 1H, 1xH7), 4.154 (m, 1H, 1xH7), 4.790 (ddd, J=9.0, 4.5, 1.0 Hz, 1H, H13β), 4.899 (s, 1H, H10α), 5.012 (s, 1H, 1xH20), 5.097 (s, 1H, 1xH20).

Hydroxy ketone **16**. To a solution of hydroxy ketone **15** (450.0 mg, 0.72 mmol) in 15 mL of CH_2Cl_2 at room temperature under N_2 was added diisopropylethylamine (1.25 mL, 7.2 mmol), followed by tetrabutylammonium iodide (265.0 mg, 0.72 mmol), and benzyloxymethylchloride (0.5 mL, 3.6 mmol). After stirring at room temperature for 24 h, another 1.25 mL (7.2 mmol) of diisopropylethylamine followed by 0.5 mL (3.6 mmol) of benzyloxymethylchloride was added. The solution was stirred at room temperature for another 24 h, and then was heated to 40 °C for 2 h. After being recooled to room temperature, the solution was diluted with 50 mL of THF and 5 mL of MeOH. Then a 0.1 N aqueous solution of NaOH (10 mL, 1.0 mmol) was added. After stirring at room temperature for 1.5 h, the solution was diluted with 100 mL of 20% EtOAc in hexane,

and poured into 50 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with 20% EtOAc in hexane (50 mL, 3 times). The organic layers were combined, washed with 50 mL of a saturated aqueous NH_4Cl solution, 50 mL of a saturated aqueous $NaHCO_3$ solution, and then dried over Na_2SO_4. Removal of the solvent followed by flash chromatography purification (20% EtOAc/hexane) gave 430.0 mg (85% yield) of the desired hydroxy ketone **16** as a colorless oil.

16: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.140 (s, 3H, TBS CH_3), 0.150 (s, 3H, TBS CH_3), 0.636 (qd, J=8.0, 4.0 Hz, 6H, TES CH_2), 0.939 (d, J=7.0 Hz, 3H, Me19), 0.949 (t, J=8.0 Hz, 9H, TES CH_3), 0.967 (s, 9H, TBS *t*-Bu), 1.078 (s, 3H, Me17), 1.202 (s, 3H, Me16), 1.450 (ddd, J=15.0, 8.5, 5.0 Hz, 1H, H14α), 1.661 (t, J=6.0 Hz, 1H, OH20), 1.695-1.821 (m, 2H, 2xH6), 1.910 (d, J=1.0 Hz, 3H, Me18), 2.055 (m, 1H, 1xH5), 2.174 (m, 1H, H1), 2.258 (m, 1H, 1xH5), 2.317 (m, 1H, H14β), 2.473 (dd, J=10.0, 7.0 Hz, 1H, H3), 3.100 (dq, J=7.0, 7.0 Hz, 1H, H8α), 3.615-3.693 (m, 2H, 2xH7), 3.967 (dd, J=10.0, 3.0 Hz, 1H, H2β), 4.548 (d, J=12.0 Hz, 1H, 1HxBOM), 4.596 (d, J=12.0 Hz, 1H, 1HxBOM), 4.601 (d, J=7.0 Hz, 1H, 1HxBOM), 4.710 (d, J=7.0 Hz, 1H, 1HxBOM), 4.836 (br td, J=8.5, 1.0 Hz, 1H, H13β), 4.868 (s, 1H, H10α), 5.009 (br s, 1H, 1xH20), 5.014 (br s, 1H, 1xH20), 7.277-7.346 (m, 5H, 5HxBOM); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) -5.34, -4.69, 4.61, 6.48, 15.57, 17.88, 18.03, 25.74, 26.01, 30.05, 32.40, 32.73, 36.60, 37.27, 47.32, 53.74, 62.22, 69.32, 69.69, 79.84, 82.51, 94.65, 113.60, 127.57, 127.70, 128.52, 135.67, 138.25, 141.04, 148.02, 215.16.

Keto aldehyde **17**. To a mixture of hydroxy ketone **16** (130.0 mg, 0.186 mmol) and 150 mg of 3A°

molecular sieves in 5 mL of CH_2Cl_2 at room temperature under N_2 was added 4-methyl- morpholine (65.0 mg, 0.55mmol) followed by tetrapropylammonium perruthenate (7.0 mg, 0.02 mmol). After stirring at room temperature for 2 min., the mixture was filtered through a short pad of silica gel. The silica gel was washed with 50 mL of 10% EtOAc in hexane. Removal of the solvent gave 116.8 mg (90% yield) of desired keto aldehyde **17** as a colorless oil, which was used without further purification.

17. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.128 (s, 3H, TBS CH_3), 0.139 (s, 3H, TBS CH_3), 0.615 (qd, J=8.1, 2.1 Hz, 6H, TES CH_2), 0.919 (d, J=6.6 Hz, 3H, Me19), 0.948 (t, J=8.1 Hz, 9H, TES CH_3), 0.952 (s, 9H, TBS *t*-Bu), 1.058 (s, 3H, Me17), 1.197 (s, 3H, Me16), 1.413 (m, 1H, H14α), 1.900 (br s, 3H, Me18), 2.159 (m, 1H), 2.239-2.387 (m, 2H), 2.422-2.700 (m, 4H), 3.094 (qd, J=6.6, 6.6 Hz, 1H, H8), 3.954 (dd, J=9.6, 2.7 Hz, 1H, H2), 4.513 (d, J=12.0 Hz, 1H, 1HxBOM), 4.574 (d, J=7.2 Hz, 1H, 1HxBOM), 4.595 (d, J=12.0 Hz, 1H, 1HxBOM), 4.704 (d, J=7.2 Hz, 1H, 1HxBOM), 4.821 (br t, J=8.4 Hz, 1H, H13), 4.848 (s, 1H, H10), 4.905 (br s, 1H, 1xH20), 5.029 (br s, 1H, 1xH20), 7.278-7.360 (m, 5HxBOM), 9.724 (t, J=1.5 Hz, 1H, CHO).

Alkene **18**. A 0.08 M solution of BaO in MeOH (10.0 mL) was added to keto aldehyde **17** (116.8 mg, 0.167 mmol) at room temperature under N_2. After stirring at room temperature for 9 h, the solution was concentrated under reduced pressure. Then 30 mL of EtOAc and 20 mL of a saturated aqueous $NaHCO_3$ solution were added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (30 mL, 5 times). The organic layers were combined and dried over Na_2SO_4. Removal of the solvent gave 110.0 mg (94% yield) of the crude

product as a pale yellow oil, which was used without further purification.

To a solution of the above crude product (110.0 mg, 0.158 mmol) in 2 mL of pyridine at 0 °C under N_2 was added TESOTf (0.11 mL, 0.47 mmol). After stirring at 0 °C for 1 h, the solution was diluted with 30 mL of 10% EtOAc in hexane, and poured into 30 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with 10% EtOAc in hexane (30 mL, 3 times). The organic layers were combined and dried over Na_2SO_4. Removal of the solvent followed by flash chromatography purification (2% EtOAc/hexane) gave 100.0 mg (78% overall yield from hydroxy ketone **16**) of the desired alkene **18** as a colorless oil.

18: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.099 (s, 3H, TBS CH_3), 0.131 (s, 3H, TBS CH_3), 0.565 (q, J=8.0 Hz, 6H, TES CH_2), 0.635 (qd, J=8.0, 2.5 Hz, 6H, TES CH_2), 0.925 (s, 9H, TBS *t*-Bu), 0.943 (t, J=8.0 Hz, 9H, TES CH_3), 0.960 (s, 3H, Me17), 0.995 (t, J=8.0 Hz, 9H, TES CH_3), 1.136 (s, 3H, Me19), 1.155 (s, 3H, Me16), 1.561 (m, 1H, H6β), 1.637 (dd, J=15.0, 5.5 Hz, 1H, H14α), 1.794 (br d, J=9.0 Hz, 1H, H1), 1.915 (m, 1H, H6α), 2.043 (d, J=1.5 Hz, 3H, Me18), 2.106-2.162 (m, 2H, 2xH5), 2.500 (dt, J=15.0, 9.0 Hz, 1H, H14β), 3.244 (br d, J=4.0 Hz, 1H, H3), 3.785 (br dd, J=4.0, 1.0 Hz, 1H, H2β), 4.173 (dd, J=11.0, 4.5 Hz, 1H, H7α), 4.565 (m, 1H, H13β), 4.579 (s, 2H, 2HxBOM), 4.680 (d, J=7.0 Hz, 1H, 1HxBOM), 4.703 (d, J=7.0 Hz, 1H, 1HxBOM), 4.929 (br s, 1H, 1xH20), 5.363 (s, 1H, H10α), 5.489 (t, J=2.0 Hz, 1H, 1xH20), 7.270-7.343 (m, 5H, 5HxBOM); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) -5.33, -4.54, 4.89, 5.92, 6.62, 6.71, 11.53, 17.27, 17.78, 24.95, 25.65, 31.09, 32.40, 32.79, 37.63, 37.83, 47.44, 49.34, 62.19, 68.53, 70.05, 75.00, 76.36, 78.90, 93.74,

113.68, 127.73, 127.90, 128.54, 136.72, 137.17, 138.11, 143.93, 209.62.

Allylic alcohol **19**. To a solution of alkene **18** (80.0 mg, 0.0985 mmol) in 5 mL of CH_2Cl_2 at room temperature under N_2 was added 1.0 mL of *t*-BuOOH (90% pure, 9.8 mmol), followed by SeO_2 (109.0 mg, 0.985 mmol). After stirring at room temperature for 10 h, the solution was diluted with 50 mL of 20% EtOAc in hexane and poured into 20 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with 20% EtOAc in hexane (20 mL, 3 times). The organic layers were combined and washed with 10 mL of water, and then dried over Na_2SO_4. Removal of the solvent followed by flash chromatography purification (3% EtOAc/hexane) gave 75.0 mg (92% yield) of the desired allylic alcohol **19** as a colorless oil.

19: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.135 (s, 3H, TBS CH_3), 0.162 (s, 3H, TBS CH_3), 0.571 (q, J=8.0 Hz, 6H, TES CH_2), 0.640 (qd, J=8.0, 1.5 Hz, 6H, TES CH_2), 0.927 (s, 3H, Me17), 0.943 (s, 9H, TBS *t*-Bu), 0.959 (t, J=8.0 Hz, 9H, TES CH_3), 0.995 (t, J=8.0 Hz, 9H, TES CH_3), 1.109 (s, 3H, Me19), 1.163 (s, 3H, Me16), 1.564-1.632 (m, 2H, H6β, H14α), 1.792 (br d, J=8.5 Hz, 1H, H1), 2.108 (br, 1H, OH5), 2.123 (d, J=1.0 Hz, 3H, Me18), 2.155 (m, 1H, H6α), 2.550 (dt, J=15.0, 8.5 Hz, 1H, H14β), 3.785 (br d, J=2.0 Hz, 1H, H2β), 3.931 (br t, J=2.0 Hz, 1H, H3), 4.180 (t, J=3.0 Hz, 1H, H5β), 4.570 (s, 2H, 2HxBOM), 4.597 (dd, J=11.5, 4.5 Hz, 1H, H7α), 4.613 (br t, J=8.5 Hz, 1H, H13β), 4.675 (d, J=7.0 Hz, 1H, 1HxBOM), 4.697 (d, J=7.0 Hz, 1H, 1HxBOM), 5.166 (t, J=2.0 Hz, 1H, 1xH20), 5.414 (s, 1H, H10α), 5.742 (t, J=2.0 Hz, 1H, 1xH20), 7.268-7.347 (m, 5H, 5HxBOM).

Diol mesylate **20**. To a solution of allylic alcohol **19** (14.0 mg, 0.017 mmol) in 0.7 mL of pyridine at 0 °C under N_2 was added MsCl (0.05 mL, 0.645 mmol). The solution was stirred at 0 °C for 2 h. Then 1.5 mL of Et_2O followed by 0.22 mL (0.034 mmol) of a 0.157 M solution of OsO_4 in THF was added. The mixture was kept at -20 °C for 12 h, and then was diluted with 5 mL of THF. Next, 30 mg of $NaHSO_3$ followed by 0.5 mL of H_2O was added. After stirring at room temperature for 8 h, the solution was diluted with 50 mL of EtOAc, and poured into 50 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL, 3 times). The organic layers were combined and dried over Na_2SO_4. Removal of the solvent gave 15 mg of desired diol mesylate **20** as a pale yellow oil, which was used without further purification.

20: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.122 (s, 3H, TBS CH_3), 0.173 (s, 3H, TBS CH_3), 0.558 (q, J=8.0 Hz, 6H, TES CH_2), 0.640 (qd, J=8.0, 5.0 Hz, 6H, TES CH_2), 0.949 (t, J=8.0 Hz, 9H, TES CH_3), 0.964 (s, 9H, TBS t-Bu), 0.978 (t, J=8.0 Hz, 9H, TES CH_3), 1.070 (s, 3H, Me16), 1.085 (s, 3H, Me17), 1.174 (s, 3H, Me19), 1.935 (m, 1H, H6β), 1.977-2.037 (m, 2H, H14α, H1), 2.123 (d, J=1.0 Hz, 3H, Me18), 2.244 (dt, J=15.0, 4.5 Hz, 1H, H6α), 2.316 (dt, J=14.0, 9.0 Hz, 1H, H14β), 2.381 (dd, J=10.5, 1.5 Hz, 1H, OH20), 3.147 (s, 3H, SO_2CH_3), 3.575 (d, J=6.5 Hz, 1H, H3), 3.607 (t, J=10.5 Hz, 1H, 1xH20), 3.940 (dd, J=10.5, 1.5 Hz, 1H, 1xH20), 3.990 (dd, J=6.5, 2.5 Hz, 1H, H2β), 4.133 (s, 1H, OH4), 4.228 (dd, J=11.5, 4.5 Hz, 1H, H7α), 4.613 (s, 2H, 2HxBOM), 4.766 (d, J=7.0 Hz, 1H, 1HxBOM), 4.825 (m, 1H, H13β), 4.839 (d, J=7.0 Hz, 1H, 1HxBOM), 4.895 (m, 1H, H5β), 5.276 (s, 1H, H10α), 7.298-7.357 (m, 5H, 5HxBOM).

Oxetane **21**. To a solution of the above diol mesylate **20** in 1.0 mL of toluene at room temperature under N_2 was added DBU (0.06 mL, 0.04 mmol). The solution was then heated to 120 °C (oil bath temperature) for 15 minutes, and kept at 120 °C for another 15 minutes. Removal of the solvent followed by flash chromatography purification (15% EtOAc/hexane) gave 12.5 mg of desired oxetane **21** (87% overall yield from allylic alcohol **19**) as a colorless oil.

21: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.143 (s, 3H, TBS CH_3), 0.154 (s, 3H, TBS CH_3), 0.580 (q, J=8.0 Hz, 6H, TES CH_2), 0.635 (qd, J=8.0, 2.5 Hz, 6H, TES CH_2), 0.952 (t, J=8.0 Hz, 9H, TES CH_3), 0.971 (s, 9H, TBS *t*-Bu), 0.977 (s, 3H, Me17), 0.992 (t, J=8.0 Hz, 9H, TES CH_3), 1.116 (s, 3H, Me16), 1.532 (s, 3H, Me19), 1.944 (m, 1H, H1), 1.945 (d, J=1.5 Hz, 3H, Me18), 2.000 (m, 1H, H14α), 2.030 (m, 1H, H6β), 2.407 (dt, J=15.5, 9.5 Hz, 1H, H14β), 2.465 (m, 1H, H6α), 2.990 (s, 1H, OH4), 3.050 (d, J=5.5 Hz, 1H, H3), 3.888 (dd, J=5.5, 2.5 Hz, 1H, H2β), 4.042 (dd, J=11.5, 6.5 Hz, 1H, H7α), 4.358 (d, J=8.0 Hz, 1H, H20α), 4.513 (d, J=12.0 Hz, 1H, 1HxBOM), 4.555 (ddd, J=9.5, 4.5, 1.5 Hz, 1H, H13β), 4.608 (d, J=12.0 Hz, 1H, 1HxBOM), 4.640 (d, J=8.0 Hz, 1H, H20β), 4.645 (d, J=6.5 Hz, 1H, 1HxBOM), 4.713 (d, J=6.5 Hz, 1H, 1HxBOM), 4.730 (dd, J=10.0, 4.0 Hz, 1H, H5α), 5.153 (s, 1H, H10α), 7.270-7.355 (m, 5H, 5HxBOM); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) -5.21, -4.39, 4.99, 5.77, 6.60, 6.68, 10.32, 16.28, 17.98, 24.45, 25.84, 30.73, 31.31, 37.53, 37.68, 45.36, 50.59, 58.88, 68.15, 70.28, 73.33, 74.74, 76.30, 78.73, 81.39, 86.61, 94.82, 127.69, 128.01, 128.69, 136.43, 137.67, 137.83, 207.89.

Diol **22**. To a solution of oxetane **21** (60.0 mg, 0.071 mmol) in 0.1 mL of CH_3CN at room temperature was

added 1.0 mL of a 48% HF/pyridine/CH_3CN (1:3.5:3.5) solution. After stirring at room temperature for 24 h, the solution was diluted with 50 mL of EtOAc, and poured into 20 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL, 3 times). The organic layers were combined and dried over Na_2SO_4. Removal of the solvent then gave the tetraol as a pale yellow oil, which was used without any further purification.

To a solution of the above oil in 1 mL of pyridine at room temperature was added TESCl (0.06 mL, 0.355 mmol). After stirring at room temperature for 21 h, the solution was diluted with 10 mL of EtOAc, and poured into 20 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL, 3 times). The organic layers were combined and dried over Na_2SO_4. Removal of the solvent followed by chromatography purification (5% EtOAc/hexane) gave the desired diol **22** (48.0 mg, 93% overall yield) as a colorless oil.

22: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.538 (qd, J=8.0, 1.0 Hz, 6H, TES CH_2), 0.707 (q, J=8.0 Hz, 6H, TES CH_2), 0.919 (t, J=8.0 Hz, 9H, TES CH_3), 1.001 (s, 3H, Me17), 1.011 (s, 3H, Me16), 1.026 (t, J=8.0 Hz, 9H, TES CH_3), 1.605 (s, 3H, Me19), 1.964-2.037 (m, 3H, H1, H14α, H6β), 2.019 (d, J=1.5 Hz, 3H, Me18), 2.392 (m, 1H, H6α), 2.452 (m, 1H, H14β), 3.090 (d, J=6.0 Hz, 1H, H3), 3.150 (s, 1H, OH4), 3.873 (dd, J=6.0, 3.0 Hz, 1H, H2), 3.988 (dd, J=11.5, 7.5 Hz, 1H, H7α), 4.140 (d, J=3.0 Hz, 1H, OH10), 4.396 (d, J=7.5 Hz, 1H, H20α), 4.527 (d, J=11.5 Hz, 1H, 1Hx BOM), 4.599 (br m, 1H, H13β), 4.621 (d, J=11.5 Hz, 1H, 1HxBOM), 4.626 (d, J=7.5 Hz, 1H, H20β), 4.656 (d, J=6.5 Hz, 1H, 1HxBOM), 4.729 (d, J=6.5 Hz, 1H, 1HxBOM), 4.787 (dd, J=9.5, 4.0 Hz, 1H, H5α), 5.106 (d,

J=3.0 Hz, 1H, H10), 7.284-7.363 (m, 5H, 5HxBOM); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 4.672, 4.945, 6.433, 6.645, 9.878, 16.509, 23.976, 29.500, 30.775, 31.791, 37.406, 45.222, 50.655, 58.288, 68.259, 70.292, 73.494, 74.754, 75.133, 78.639, 81.158, 86.804, 94.907, 127.687, 128.067, 128.704, 136.337, 137.597, 140.025, 212.474.

Bis-acetate **23**. To a solution of diol **22** (5.0 mg, 0.007 mmol) in 0.5 mL of pyridine at room temperature was added 4-dimethylaminopyridine (2.0 mg, 0.014 mmol) followed by Ac_2O (0.01 mL, 0.1 mmol). After stirring at room temperature for 21 h, the solution was diluted with 10 mL of EtOAc, and poured into 20 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL, 3 times). The organic layers were combined and dried over Na_2SO_4. Removal of the solvent followed by flash chromatography purification (5% EtOAc/hexane) gave the desired *bis*-acetate **23** (3.4 mg, 60% yield) as a colorless oil.

23: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.518 (q, J=8.0, 1.0 Hz, 6H, TES CH_2) 0.600 (qd, J=8.0, 5.0 Hz, 6H, TES CH_2), 0.912 (t, J=8.0 Hz, 9H, TES CH_3), 0.951 (t, J=8.0 Hz, 9H, TES CH_3), 1.042 (s, 3H, Me17), 1.109 (s, 3H, Me16), 1.484 (m, 1H, H14α), 1.653 (s, 3H, Me19), 1.918(ddd, J=14.0, 10.5, 2.5 Hz, 1H, H6β), 2.107 (d, J=1.0 Hz, 3H, Me18), 2.138 (s, 3H, OAc10), 2.162-2.207 (m, 2H, H1, H14β), 2.538 (m, 1H, H6α), 2.626 (s, 3H, OAc4), 3.628 (d, J=6.5 Hz, 1H, H3), 3.999 (dd, J=6.5, 2.5 Hz, 1H, H2), 4.496 (d, J=12.0 Hz, 1H, 1Hx BOM), 4.538 (d, J=8.5 Hz, 1H, H20β), 4.578-4.627 (m, 3H, H7α, H20α, 1HxBOM), 4.652 (d, J=6.5 Hz, 1H, 1HxBOM), 4.709 (m, 1H, H13β), 4.733 (d, J=6.5 Hz, 1H, 1HxBOM), 4.943 (dd, J=9.5,

2.5 Hz, 1H, H5α), 6.394 (s, 1H, H10), 7.284-7.369 (m, 5H, 5HxBOM).

1-Deoxy-baccatin III. To a solution of *bis*-acetate **23** (3.4 mg, 0.0042 mmol) in 0.5 mL of EtOAc and 0.5 mL of *t*-BuOH at room temperature was added 4.0 mg of 10% Pd on carbon. After stirring under H_2 for 45 min., the mixture was diluted with 10 mL of EtOAc, and filtered through a short pad of celite. Removal of the solution gave a colorless oil, which was then dissolved in 0.5 mL of $CHCl_3$, and loaded onto a column (silica gel). After 2 h at room temperature, the column was washed with EtOAc. Removal of the solvent then gave the desired crude product, which was used without any further purification.

To a solution of the above crude product in 0.5 mL of pyridine at room tempeature was added 4-pyrrolidino-pyridine (1.8 mg, 0.012 mmol) followed by 0.5 mL (0.5 mmol) of a 1.0 M solution of BzCl in pyridine (0.5 mL). After stirring at room temperature for 26 h, the solution was diluted with 10 mL of EtOAc, and poured into 20 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL, 3 times). The organic layers were combined and dried over Na_2SO_4. Removal of the solvent then gave the crude benzoate, which was used without any further purification.

To a solution of the above crude benzoate in 0.1 mL of CH_3CN at room temperature was added 0.5 mL of a 48% HF/pyridine/CH_3CN (1:3.5:3.5) solution. After stirring at room temperature for 27 h, the solution was diluted with 10 mL of EtOAc, and poured into 20 mL of a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL, 3 times). The organic layers were combined and

dried over Na_2SO_4. Removal of the solvent followed by flash chromatography purification (60% EtOAc/hexane) gave the desired **1-deoxy-baccatin III** (1.4 mg, 59% overall yield from *bis*-acetate 23).

1-Deoxy-baccatin III: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.069 (s, 3H, Me17), 1.204 (s, 3H, Me16), 1.667 (s, 3H, Me19), 1.730 (ddd, J=15.0, 7.5, 1.0 Hz, 1H, H14α), 1.890 (ddd, J=15.0, 6.0, 2.0 Hz, 1H, H6β), 1.978 (d, J=5.5 Hz, 1H, OH13), 2.034 (ddd, J=9.0, 3.5, 1.0 Hz, 1H, H1), 2.085 (d, J=1.0 Hz, 3H, Me18), 2.227 (s, 3H, OAc10), 2.290 (s, 3H, OAc4), 2.387 (d, J=4.5 Hz, 1H, OH7), 2.516 (ddd, J=15.0, 10.0, 9.0 Hz, 1H, H14β), 2.583 (ddd, J=15.0, 10.0, 7.0 Hz, 1H, H6α), 3.738 (d, J=6.5 Hz, 1H, H3α), 4.156 (dd, J=8.5, 1.0 Hz, 1H, H20β), 4.373 (d, J=8.5 Hz, 1H, H20α), 4.471 (ddd, J=10.0, 7.0, 4.5 Hz, 1H, H7α), 4.712 (dddd, J=10.0, 7.5, 5.5, 1.0 Hz, 1H, H13β), 5.023 (ddd, J=9.5, 2.0, 1.0 Hz, 1H, H5α), 5.643 (dd, J=6.5, 3.5 Hz, 1H, H2β), 6.320 (s, 1H, H10α), 7.472 (t, J=8.0 Hz, 2H, benzoate-*m*), 7.597 (dd, J=8.0, 1.0 Hz, 1H, benzoate-*p*), 8.085 (dd, J=8.0, 1.0 Hz, 2H, benzoate-*o*).

In view of the above, it will be seen that the several objects of the invention are achieved.

As various changes could be made in the above compositions without departing from the scope of the invention, it is intended that all matter contained in the above description be interpreted as illustrative and not in a limiting sense.